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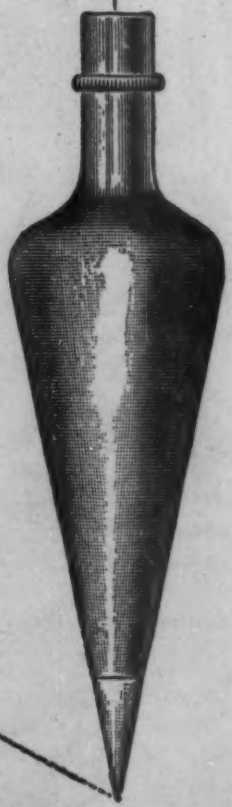

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THE ROLE OF EXUDATE LOSSES IN THE PROTEIN AND ELECTROLYTE IMBALANCE OF BURNED PATIENTS*

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INTRODUCTION

SECONDARY TO A SEVERE SKIN BURN, derangements of metabolism occur in organs and tissues far removed from the site of injury. For purposes of description these consist of the changes in distribution of the body fluids, the shifts in osmotic equilibrium and concentrations of electrolytes, and the alterations in intermediary metabolism and hormonal equilibrium. The expansion of body water available for the solution of extracellular ions and the shift of plasma protein from the intravascular to the extravascular compartment, as a result of the capillary damage engendered by the injury, have already been described.[1, 2] With these shifts in fluid and protein there must obviously be a re-distribution of electrolytes. The re-distribution within the burned tissue has been described.[3] This re-distribution occurs not only between plasma and the interstitial fluid of the burned area and between burned cells and their immediate fluid environment, but also presumably in the undamaged areas of the body.

The shift of cell chemistry and the changes in intermediary metabolism cannot be determined without a strict accounting of the constituents. To the measurement of the concentration of the various substances in the body fluids must be added the metabolic balance. By this is meant quantitative measure-

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ment of input and output by all routes, adequate to plot a balance sheet indicating the retention, or lack thereof, of each substance injected or ingested.

In the burned patient, a complete metabolic balance cannot be reconstructed if the output is calculated from analyses of the urine and feces alone. Hirshfeld, *et al.*, have shown that large quantities of nitrogen may be lost in the exudate of the wounds.[4] Keyser[5] has similarly measured nitrogen losses relative to intake and output by other routes.

In the present study this nitrogen loss is confirmed and the details elaborated; the electrolyte exuding from the surface is measured, and a complete balance sheet constructed; a tentative interpretation of the interrelationships is also presented.

I. METHODS

Balances. Immediately after onset of fluid therapy and dressing of the wounds in the Emergency Ward, the burned patients were moved to the Surgical Metabolic Ward, where quantitative exudate, urine, and feces collections were done, together with accurate measurements of intake. The intake data are based, in the case of food, on weighed portions and in the case of intravenous or tube feedings, on intake records and, when necessary, analysis. The Sherman tables were accepted for the protein and electrolyte content of the foods; in a few isolated instances food analyses were carried out. For an occasional patient whose feces were not measured, the nitrogen output has been estimated, because in those in whom the fecal nitrogen was measured, a remarkably constant value was found. Where occasional urine specimens were lost or inadvertently discarded the values are interpolated.

The administration of whole blood presents an enigma in the calculation of balance studies. It is apparent that the proteins and electrolytes of plasma given intravenously are readily available to metabolic processes; it is not so apparent how the body handles the proteins and electrolytes of red cells given in transfusion. The protein and ionic content of erythrocytes is not available for general tissue metabolism until the red cell breaks down; yet having been given intravenously it cannot be neglected in intake, since red cells may exert an immediate "sparing" effect on protein otherwise destined for red cell production. In the data presented herein, red cells have been counted as simple intake. It is admitted that this produces some irregularities in the curves. The intake is recorded on the day the cells were given.

Exudate Losses. Dressings, and sheets or pillows stained with transudate, were saved; the soluble constituents were salvaged by solution in large tubs of distilled water. This solution was then analyzed. New or washed gauze was used. "Blanks" carried out on the gauze showed a negligible content of nitrogen, potassium, sodium and chloride. Recovery of inorganic ions by this method is accurate within 5 per cent. The same cannot be said for nitrogen, even early in the course of a burn the odor of NH_3 may be present, indicating bacterial formation of ammonia and consequent loss of N by volatilization. The N figures serve only as a first approximation of nitrogen loss via the

exudate; it would appear from the consistently high nitrogen values for exudate that losses by volatilization as NH_3 are not excessive.

Material Studied—Nitrogen balances are available on 12 patients. One had a minor burn and was studied as a control (Case 264); two suffered partial thickness burns of major extent (Cases 196 and 254); five suffered extensive full thickness burns and survived; four others succumbed. Of the 12 studied, exudate data are available on 11 patients.

TABLE I.—*Nitrogen Balance; Minor Burn.*

Period		Intake	Output				Balance	Exudate	
Dates (Inc.)	Days	Diet +I.V. Gm.	Urine Gm.	Feces Gm.	Exudate Gm.	Total Gm.	Gm.	% of Intake	% of Output
Pt. 264; female; age 41; per cent burn: 5½% total; 0% full thickness; 10/8/45									
10/8	1		1.7	1.0(Est.)	0.5	3.2			
10/9	1	16.0	11.6	1.0	0.6	13.2	+2.8	3.8	4.6
10/10	1	14.5	12.7	1.0	0.6	14.3	+0.2	4.1	4.2
10/11	1	12.0	15.0	1.0	0.3	16.3	−4.3	2.5	1.8
10/12	1	17.5	16.0	1.0	0.0	17.0	+0.5		
10/13	1	24.3	18.1	1.0	0.0	19.1	+5.2		
10/14	1	24.3	19.6	1.0	0.0	20.6	+3.7		
10/15	1	15.2	10.0	1 0	0.0	11.0	+4.2		
10/9–10/15	7	123.8	103.0	7.0	1.5	111.5	+12.3	1.21	1.35

Sodium balances are available on ten patients. They were: the patient with the minor burn studied as a control (Case 264), the two patients (Cases 196 and 254) suffering partial thickness burns, the four patients (Cases 210, 217, 260 and 269) having extensive full thickness burns and surviving, and three

TABLE II.—*Nitrogen Balance; Partial-Thickness Burn.*

Period		Intake	Output				Balance	Exudate	
Dates (Inc.)	Days	Diet +I.V. Gm.	Urine Gm.	Feces Gm.	Exudate Gm.	Total Gm.	Gm.	% of Intake	% of Output
Pt. 254; male; age 38; per cent burn: 45% total; 5% full thickness; 5/29/45.									
5/29–6/8	10+	290.4	271.7	10.7	30.1	312.5	−22.1	10.3	9.6
6/9–6/18	10	273.2	292.5	15.3	22.7	330.5	−57.3	8.3	6.9
6/19–6/28	10	305.5	288.0	20.2	11.0	319.2	−13.7	3.6	3.5
6/29–7/8	10	301.9	247.2	22.4	9.0	278.6	+23.3	3.0	3.2
7/9–7/18	10	303.3	279.0	23.2	1.2	303.4	−0.1	0.4	0.4
7/19–7/28	10	307.3	186.6	15.0	0	201.6	+105.7	0.0	0.0

of the patients (Cases 234, 262 and 268), who succumbed. In seven of these patients the exudate sodium losses are available.

Chloride balances are available on eight patients: the one locally burned studied as a control, one with partial thickness burn, the four with extensive full thickness burns surviving and two of the fatally burned. Exudate chloride losses were measured in five.

Potassium balances are available on nine cases, the same patients on whom the sodium balances were done with the exception of one of the partial thickness burns (Case 196). Exudate potassium losses are available in seven of these patients.

II. RESULTS

A. Nitrogen Balance

Findings. The nitrogen balance in a patient with a minor burn is shown in Table I. The patient suffered a negligible burn of one arm and serves as a control. During the week in which she was studied she was in positive nitrogen balance on all days save one. The balance for the over-all period is plus 12.3 Gm., an average of a little more than 1.5 Gm. a day. Since 1.5 Gm. of nitrogen represent approximately 10 Gm. of protein or 30 Gm. of muscle tissue it is apparent that this nitrogen positivity is negligible and would not be discernible by weight change. This patient maintained an oral regimen from the time of entry and at no time could be considered as undergoing starvation.

TABLE III.—*Nitrogen Balance; Full Thickness Burns; Survival.*

Period		Intake	Output				Balance	Exudate	
Dates (Inc.)	Days	Diet + I.V. Gm.	Urine Gm.	Feces Gm.	Exudate Gm.	Total Gm.	Gm.	% of Intake	% of Output
Pt. 164; male; age 32; per cent burn: 36% total; 7% full thickness; 6/14/44.									
6/14–6/24	10+	369.4	295.9	12.2	27.0	335.1	+34.3	7.3	8.1
6/25–7/4	10	248.9	297.7	13.4	23.6	334.7	−85.8	9.5	7.1
7/5–7/14	10	183.4	196.4	14.8	13.9	225.1	−41.7	7.6	6.2
7/15–7/24	10	227.2	177.1	20.9	5.9	203.9	+23.3	2.6	2.9
7/25–8/3	10	303.1	212.6	19.8	5.5	237.9	+65.2	1.8	2.3
Pt. 269; male; age 60; per cent burn: 27% total; 20% full thickness; 11/2/45.									
11/2–11/12	10+	211.2	211.3		40.0	251.3	−40.1	19.0	16.0
11/13–11/23	11	305.4	297.2		38.0	335.2	−29.8	12.4	11.3

In Table II is shown the nitrogen balance of one of the two patients with burns predominantly of partial thickness,* (Case 254). The patient is initially in negative nitrogen balance, reverting to positive balance after the fortieth day. The loss of nitrogen in the exudates falls off rapidly with healing of the wounds.

In Tables III, IV and V are shown the nitrogen balances on five extensively and deeply burned patients (Cases 164, 269, 210, 217 and 260) who survived their burns. Three of these patients (Cases 164, 210 and 217—Tables III and IV) show a characteristic pattern consisting of initially positive nitrogen balances coincident with plasma and blood therapy, followed by negative nitrogen balances lasting from 20 to 40 days, and finally yielding to positive balances as the wound closed and convalescence was completed.

Patient 260 (Table V) is unusual in that she never exhibited a consistently negative nitrogen balance in the 28 days during which her balance was measured. However, it should be noted that nitrogen balance in her first ten day period is more strongly positive than that observed in any other patient (124.2 Gm. total or 12.4 Gm. per day), and that following this initial high peak

* In these and the subsequent ten tables the nitrogen balance data are presented in periods of five or ten days' duration, depending on the length of the study. The presentation in periods is for the sake of brevity and ease of interpretation of data; analyses were done on a daily basis.

(presumably due to plasma therapy) the nitrogen retention drops to 46.2 and 12.0 Gm. of positive balance in her subsequent two periods. Although none of her values fall below the zero line the curve is parallel to that of the other patients of this group at a quantitatively higher level.

TABLE IV.—*Nitrogen Balance; Full Thickness Burns; Survival.*

Period		Intake	Output				Balance	Exudate	
Dates (Inc.)	Days	Diet + I.V. Gm.	Urine Gm.	Feces Gm.	Exudate Gm.	Total Gm.	Gm.	% of Intake	% of Output
Pt. 210; female; age 34; per cent burn: 31% total; 25% full thickness; 12/28/44.									
12/28–1/7	10+	287.1	207.4	13.6	20.2	241.2	+45.9	7.0	8.4
1/8–1/17	10	332.7	317.7	16.7	32.6	367.0	−34.3	9.8	8.9
1/18–1/27	10	189.5	207.9	9.7	55.3	272.9	−83.4	29.1	20.2
1/28–2/6	10	132.0	123.7	7.4	24.9	156.0	−24.0	18.9	16.0
2/7–2/16	10	154.9	106.6	8.3	43.3	158.2	− 3.3	28.0	27.4
2/17–2/26	10	128.3	76.0	4.4	35.3	115.7	+12.6	27.5	30.4
2/27–3/8	10	166.4	84.6	7.0	21.2	112.8	+53.6	12.7	18.8
3/9–3/18	10	130.5	71.1	7.5	24.9	103.5	+27.0	19.1	24.1
3/19–3/28	10	99.5	48.8	6.0	15.2	70.0	+29.5	15.3	21.8
3/29–4/7	10	145.8	84.8	7.2	19.2	111.2	+34.6	13.2	17.2
4/8–4/17	10	122.9	68.6	10.0	16.3	94.9	+28.0	13.3	17.2
4/18–4/27	10	129.8	52.8	7.1	5.3	65.2	+64.6	4.1	8.1
4/28–5/4	7	107.1	41.5	8.9	4.6	55.0	+52.1	4.3	8.4
Pt. 217; female; age 26; per cent burn: 78% total; 45% full thickness; 1/12/45.									
1/12–1/22	10+	387.7	281.5		49.3	330.8	+56.9	12.7	14.9
1/23–2/1	10	306.5	333.2		47.9	381.1	−74.6	15.6	12.5
2/2–2/11	10	327.0	284.2		61.4	345.6	−18.6	18.8	17.8
2/12–2/21	10	372.7	208.6		84.6	293.2	+79.5	22.7	28.9
2/22–3/3	10	336.5	145.4		59.1	204.5	+132.0	17.6	29.0
3/4–3/13	10	261.7	150.3		59.1	209.4	+52.3	22.6	28.3
3/14–3/23	10	242.2	121.0		45.8	166.8	+75.4	18.9	27.5
3/24–4/2	10	227.7	114.2		43.3	157.5	+70.2	19.0	27.5
4/3–4/12	10	209.2	113.5		57.3	170.8	+38.4	27.4	33.5
4/13–4/22	10	210.9	111.2		37.7	148.9	+62.0	17.9	25.3

The nitrogen balances of four patients who succumbed to extensive burns are not significantly different for the period they lived from those already described who survived.

Interpretation. A normal adult on ordinary diet, at work, neither gaining nor losing weight, is in essentially zero nitrogen balance. A growing child,

TABLE V.—*Nitrogen Balance; Full Thickness Burn; Survival.*

Period		Intake	Output				Balance	Exudate	
Dates (Inc.)	Days	Diet + I.V. Gm.	Urine Gm.	Feces Gm.	Exudate Gm.	Total Gm.	Gm.	% of Intake	% of Output
Pt. 260; female; age 27; per cent burn: 28% total; 12% full thickness; 8/13/45.									
8/13–8/23	10+	261.8	97.8	10.8	29.0	137.6	+124.2	11.1	21.1
8/24–9/2	10	280.8	188.6	20.1	25.9	234.6	+46.2	9.2	11.0
9/3–9/10	8	203.1	150.0	15.8	25.3	191.1	+12.0	12.5	13.2

or an adult who is gaining weight in terms of muscle mass, is in positive nitrogen balance, the extent of positivity being a function of the amount of protein-containing tissue formed per unit of time. An adult who is gaining weight in terms of fat or water-storage may be in zero or even slightly negative nitrogen balance. A normal adult who is losing weight in terms of fat alone may also be in zero or only slightly negative nitrogen balance; if the

loss of weight is at the expense of muscle and parenchymatous tissues which contain a significant fraction of protein, an adult who is losing weight will be in definitely negative nitrogen balance. Following non-specific trauma such as a fracture or a surgical operation, patients are often found to be in negative nitrogen balance for several days to several weeks. This period of negative nitrogen balance appears to be generally proportional to the extent of the trauma, providing the subject is in good health at the outset.[6] It probably results from an endocrine adjustment involving pituitary and adrenal function, and may represent destruction of tissue, though evidence is not always available as to which tissues are involved.

Realizing that patients tend to develop a negative nitrogen balance after trauma, one may inquire why so many of these burned patients show a strongly positive nitrogen balance in the first five days; this is the characteristic finding in all the extensive burns. The explanation is to be found in the method of treatment employed. From the evidence available it is likely that blood proteins given intravenously in plasma are not as readily available for conversion into tissue or for oxidation as energy as are amino acids given intravenously or perhaps whole proteins by mouth.[7] When plasma proteins are administered intravenously the protein molecules remain intact for varying lengths of time before they are hydrolyzed by enzymatic processes and either oxidized or reconstituted as tissue protein. Thus it is possible to place a patient who is in negative nitrogen balance in transiently positive nitrogen balance by the rapid intravenous administration of whole plasma protein. The period of nitrogen positivity may last only as long as the whole protein is given, yielding to negative balance as the protein-nitrogen is excreted. This positive nitrogen balance is an artefact and does not indicate tissue synthesis unless it is accompanied by positive potassium and phosphorus balances, and can be demonstrated to produce weight-gain independent of water-accumulation.

All the extensive burns in this series were treated initially by plasma therapy. Only in two cases (254 and 269) did the loss of nitrogen in the urine in the first days after injury outstrip the administration of nitrogen as plasma, to produce a negative nitrogen balance.

The starvation factor does not loom large in any of these patients since their daily nitrogen intakes average well over 15 Gm. This represents approximately 90 Gm. of protein, an average figure for adult dietary protein intake, though unquestionably below the optimum for burned patients. It is also of interest that the nature of the balance—whether positive or negative—bears little relation to the nitrogen intake figure. Some of the lowest ten-day intakes recorded in these patients are accompanied by positive balances. Likewise, negative balances may co-exist with very high nitrogen intakes, for example patients 164, 210 and 217, each in their second period.

During the nitrogen negative period, from ten to 60 days following the burn, the degree of nitrogen negativity is variable, the maxima lying in the vicinity of 10 Gm. of nitrogen a day. It is of interest to calculate what this

means in terms of body weight. Ten Gm. of nitrogen lost a day signifies a loss of 60 to 65 Gm. of protein a day. Since the cellular structures of the body, such as muscle, consist approximately of 66 per cent water and 34 per cent protein and salts it becomes clear that when 62.5 Gm. of protein are lost this represents the loss of about 190 Gm. of tissue. Thus in a ten day period a patient may, with this degree of nitrogen negativity, lose approximately two Kg. of cellular protein-containing tissue. When one considers that utilization of fat depots is occurring simultaneous with this loss of nitrogen it is apparent that a negative nitrogen balance amounting to 8 to 10 Gm. a day represents a marked loss of body tissues. Were such a process to continue unchecked, starvation, depletion, cachexia and death would be the outcome.

Since all of these patients were in a state of partial caloric starvation during the first seven to ten days after the burn, the nitrogen-sparing action of carbohydrate calories is not apparent; the earliest possible resumption of high-caloric diets is of unquestioned importance in the management of the patient.

The Significance of the Exudate in Nitrogen Loss. In ten of the 12 nitrogen balance studies the loss of nitrogen in the exudate was quantitated. In the minor control burn (264, Table I) it will be observed that exudate loss constitutes an insignificant fraction of the total loss of nitrogen—less than 2 per cent, taking the over-all figures for the week. On the days in which exudate nitrogen loss occurred, which was the case in only the first four days of the patient's hospitalization, nitrogen loss comprised approximately 4 per cent of the output and 3 per cent of the intake. In patient 254 (Table II) a patient suffering a partial thickness burn of 45 per cent of his body surface (5 per cent being of full thickness), in the early period—his first ten days—nitrogen loss through the exudate accounted for 10 per cent of his nitrogen output and equalled approximately 10 per cent of the intake. This was largely a superficial burn, and during the early after-burn period fluid of relatively high protein content was lost from the weeping surface and the nitrogen lost thereby is significant. However, this loss of nitrogen soon ceases, and by the patient's thirtieth day nitrogen loss through the exudate is insignificant, finally disappearing completely on the fiftieth day.

In contrast to the superficial burns, the extensive full thickness burns (Tables III through V) consistently show a loss of nitrogen through the exudate less in the early phase than later in their course. In patients 164 and 210, for instance, in the early period, approximately 8 per cent of the output and 7 per cent of the nitrogen intake was lost in exudate. However, as time goes by in the full thickness burn, the necrotic skin sloughs, exposing infected granulation tissue which exudes a serous and purulent exudate. The result, in contrast to the partial thickness burn, is a rising nitrogen loss in the exudate, reaching proportions as high as 25 to 30 per cent of the total output and a like fraction of the intake, between the thirtieth and seventieth hospital days. During these times of high nitrogen loss through the exudate as much as 55 Gm. of nitrogen may be found in the exudate in a ten-day period. This is consider-

ably more than is often observed in the urine of a healthy individual and approximates in protein equivalance (30 Gm. daily) a subsistence adult diet. It is therefore clear that this exudate loss imposes a sizeable load on nitrogen intake and nitrogen stores. It is of interest in patient 210, Table IV, that during her third ten-day period in the hospital she lost more nitrogen through her exudate than she lost through her urine later on at the end of her stay.

In most instances the extent of negative nitrogen balance is greater than the exudate loss; the negativity of the nitrogen balance cannot be laid entirely at the door of exudate. These data suggest but do not prove that were the exudate nitrogen to remain within the patient, the patient would still be in negative nitrogen balance. The negative nitrogen balance observed in these patients represents a biologic phenomenon not to be explained solely on the basis of starvation or loss through a large open wound. Though obscured in many instances by the plasma-produced positivity of the early days in the hospital, these burned patients consistently show a period of nitrogen negativity akin to that described for other forms of trauma.[6, 8] The exudate loss of nitrogen, while quantitatively significant, furthers, but does not produce, this negative nitrogen balance.

B. Sodium Balance

Findings. The balance of sodium tends to be positive in the first few days after injury, followed by a period of negative balance which may yield to a positive balance later in the patient's convalescence (Tables VI, VII, VIII and IX). The extent of this early positive sodium balance ranges from six to 48 Gm. for the first three-day period. During the subsequent seven to 17 days all but one of the patients show a negative sodium balance. The minor burn studied as a control (Case 264, Table VI) is in essentially zero sodium balance throughout her stay.

The intake of sodium during the first three to five days may be from 5 to 20 Gm. a day. This results not only from saline given by vein or by mouth but also from the sodium in plasma which contains approximately 2.5 Gm. of sodium per liter. Just as in the case of the nitrogen balance the early positive sodium balance is probably in part a function of this therapy, and in part a result of the avidity of the wound for sodium-containing fluid.[1]

The most striking finding relative to sodium balance is the role of the exudate. In five of the seven patients in whom exudate sodium was measured, the exudate sodium loss comprises over 45 per cent of the sodium output during at least one period of observation. The only patients in whom this is not true are those with the minor burn (Case 264) and the partial thickness burn (Case 254). In four patients the exudate sodium loss comprises over 90 per cent of the sodium output in at least one period; only one of these four survived (Case 269). In the surviving patients the blood serum sodium levels were below normal, ranging between 130 and 121 mEq/L. Of the three who died (Case 268, 234 and 262) there are several periods when the exudate sodium comprises nearly all of the output (96.5 per cent and

TABLE VI.—*Sodium, Potassium and Chloride Balances; Minor Burn.*

Period		Sodium					Potassium					Chloride		
Dates		Intake	Output			Balance	Intake	Output			Balance	Intake	Output	Balance
(Inc.)	Days	Gm.	Urine Gm.	Exudate Gm.	Exudate %	Gm.	Gm.	Urine Gm.	Exudate Gm.	Exudate %	Gm.	Gm.	Urine Gm.	Gm.
Pt. 264; female; age 41; per cent burn: 5 ½% total; 0% full thickness; 10/8/45.														
10/8	1		1.6	0.5				0.9	0.05				2.4	
10/9	1	3.1	3.2	0.5	13.5	−0.6	4.3	1.6	0.01	0.62	+2.7	3.1	4.8	−1.7
10/10	1	1.9	3.4	0.5	12.8	−2.0	3.6	2.6	0.01	0.39	+1.0	2.7	5.2	−2.5
10/11	1	1.6	2.2	0.2	8.3	−0.8	4.1	2.4	0		+1.7	2.3	3.3	−1.0
10/12	1	2.4	2.4	0.02	0.8	0	4.7	2.6	0		+2.1	3.7	3.7	0
10/13	1	3.3	3.3	0.02	0.6	0	6.0	3.3	0		+2.7	4.5	5.6	−1.1
10/14	1	3.2	3.8	0.02	0.5	−0.6	5.8	3.6	0		+2.2	4.4	6.3	−1.9
10/15	1	2.7	3.7	0.0		−1.0	6.4	3.8	0		+2.6	3.9	6.3	−2.4
10/16	1	2.4	2.4	0.0		0	5.2	3.8	0		+1.4	3.4	5.4	−2.0
10/9–10/15		18.2	22.0	1.26	5.4	−5.0	34.9	19.9	0.07	0.35	+14.9	24.6	35.2	−10.6

TABLE VII.—*Sodium, Potassium and Chloride Balances; Partial-Thickness Burn.*

Period		Sodium					Potassium					Chloride				
Dates		Intake	Output			Balance	Intake	Output			Balance	Intake	Output			Balance
Inc.	Days	Urine and Feces Gm.	Exudate Gm.	Exudate Gm.	%	Gm.	Gm.	Urine and Feces Gm.	Exudate Gm.	Exudate %	Gm.	Gm.	Urine Gm.	Exudate Gm.	Exudate %	Gm.
Pt. 254; male ; age 38; per cent burn: 45% total; 5% full thickness; 5/29/45.																
5/29–6/1	3+	54.3	31.1	4.9	13.6	+18.3	13.1	13.7	0.7	4.9	− 1.3	52.2	18.7	34.0	65.0	− 0.5
6/2–6/8	7	20.6	33.1	7.8	19.0	−20.3	38.5	37.2	1.7	4.4	− 0.4	31.7	48.3	55.2	53.2	−71.8
6/9–6/18	10	34.1	26.5	5.2	16.4	+ 2.4	62.1	52.0	2.4	4.4	+ 7.7	45.1	46.0	22.0	32.4	−22.9
6/19–6/28	10	37.2	28.1	3.9	12.2	+ 5.2	79.9	67.7	1.3	1.9	+10.9	55.1	51.6	4.8	8.5	− 1.3
6/29–7/8	10	35.0	32.1	4.1	11.3	− 1.2	95.0	70.0	0	0	+25.0	51.9	24.6	3.6	12.8	+23.7
7/9–7/18	10	40.7	36.3	1.5	3.9	+ 2.9	72.3	77.0	0	0	− 4.7	56.2	65.6	1.2	1.8	−10.6
7/19–7/28	10	36.6	27.1	0	0	+ 9.5	80.4	54.6	0	0	+25.8	55.6	52.6	0	0	+ 3.0

TABLE VIII.—*Sodium, Potassium and Chloride Balances; Full-Thickness Burns; Survival.*

Period		Sodium			Potassium			Chloride		
Dates (Inc.)	Days	Intake Gm.	Output Urine Gm.	Balance Gm.	Intake Gm.	Output Urine Gm.	Balance Gm.	Intake Gm.	Output Urine Gm.	Balance Gm.
Pt. 210; female; age 34; per cent burn: 31% total; 25% full thickness; 12/28/44.										
12/28–12/31	3	42.3	9.5	+32.8	2.5	9.3	− 6.8	43.6	3.9	+39.7
1/1–1/7	7	28.7	21.5	+ 7.2	34.5	21.6	+12.9			
1/8–1/17	10	40.0	43.2	− 3.2	66.9	58.3	+ 8.6			
1/18–1/27	10	31.4	6.8	+24.6	45.7	41.7	+ 4.0	31.9	19.5	+12.4
1/28–2/6	10				39.2	32.5	+ 6.7			
2/7–2/16	10				42.4	32.1	+10.3			
2/17–2/26	10	23.4	16.6	+ 6.8	44.6	31.1	+13.5	36.9	39.3	− 2.4
2/27–3/8	10				46.1	28.2	+17.9			
3/19–3/28	10				37.2	25.8	+11.4	23.2	33.8	−10.6
3/29–4/7	10				42.8	32.4	+10.4			
4/18–4/27	10	20.8	17.0	+ 3.8	42.7	24.2	+18.5	29.0	33.0	− 4.0
Pt. 217; female; age 26; per cent burn: 78% total; 45% full thickness; 1/12/45.										
1/12–1/15	3+	59.1	10.9	+48.2	7.1	12.5	− 5.4	73.2	12.4	+60.8
1/16–1/22	7	28.5	1.9	+26.6	46.9	35.0	+11.9	40.5	13.8	+26.7
1/23–2/1	10	39.0	21.2	+17.8	73.3	60.0	+13.3	51.9	45.9	+ 6.0
2/2–2/11	10				75.4	50.6	+24.8			
2/12–2/21	10				63.2	39.2	+24.0			

Pt. 260; female; age 27; per cent burn: 28% total; 12% full thickness; 8/13/45			Urine and Feces Gm.	Exudate Gm.	Exudate %			Urine and Feces Gm.	Exudate Gm.	Exudate %			Urine and Feces Gm.	Exudate Gm.	Exudate %	
8/13–8/16	3+	30.9	5.3	4.7	47	+20.9	4.9	5.5	1.5	21.5	− 2.1	36.0	11.4	3.9	25.5	+20.7
8/17–8/23	7	24.4		12.1			39.9		4.0			38.8		9.8		
8/24–9/2	10	33.2	42.8	11.7	21.5	−21.3	65.6	56.7	4.7	7.7	+ 4.2	53.9	53.9	14.4	21.0	−14.4
9/3–9/10	8	24.1	19.8				55.5	48.1	0	0	+ 7.4	34.7	31.0			
Pt. 269; male; age 60; per cent burn: 27% total; 20% full thickness; 11/2/45.																
11/2–11/6	4+	17.2	4.4	15.5	78	− 2.7	7 4	13.2	2.0	13.2	− 7.8	21.6 (11/3–6)	11.4	17.3	60	− 7.1
11/7–11/12	6	10.3	1.1	14.1	93	− 4.9	26.6	17.7	3.6	16.9	+ 5.3	14.6	9.3	14.5	61	− 9.2
11/13–11/23	11	28.1	10.5	27.9	73	−10.3	66.2	36.7	8.7	19.2	+20.8	34.9	35.7	40.8	53.4	−41.6

higher) with only traces of sodium in the urine. In one of these three, the blood serum sodium levels were below normal, between 136 and 118 mEq/L. In the other two, the serum sodium levels ranged at normal or above; in one it ranged from a low of 135 mEq/L on the second day to 161 mEq/L before death on the seventh day and in the other from 135 to 154 mEq/L.

Interpretation. The positive balance of sodium in the first days after injury is largely the result of the collection of edema rich in sodium in the wound and expansion of the extracellular fluid space.[1] It is only in small part due to replacement of potassium by sodium in the burned tissues.[3] The source of the additional sodium is the large volume of plasma and saline solution used in therapy.

The subsequent negative sodium balance coincides with the period of rapid shrinkage of the wound. With loss of wound edema there is also a generalized loss of the sodium-rich extracellular fluid with return of this fluid volume to normal size.[1] As the body rids itself of the excessive water, it also clears itself of sodium. The extrarenal loss of sodium in the exudate is presumably an obligatory loss, the sodium being an integral part of the extracellular fluid lost on the wound surface.

That the exudate sodium is a high percentage of the total sodium output in the extensively burned patients should not be surprising. The amount in the urine is presumably a balance between sodium reserves and renal function. If the exudate loss of sodium is large enough to encroach on the sodium reserves of the body, lowering the extracellular sodium concentration, and if the kidneys are competent, the kidneys conserve sodium, allowing only traces to be lost in the urine. This concept is based upon the finding of low sodium levels in the plasma in the surviving patients during the period when the urinary excretion of sodium was small. The fact that the plasma sodium levels were high in the two fatally burned elderly patients whose kidneys excreted but small amounts of sodium suggests a kidney insufficiency in these two. As will be described later,[9] the levels of sodium in the blood plasma of surviving extensively burned patients are uniformly low until wound healing is advanced. The low levels are not restored even by massive doses of salt and are probably the result of an endocrine compensation to the trauma and infection.[9]

The large fraction of sodium output found in the exudate makes it obvious that sodium balance data in burned patients must include measurement of the exudate.

C. Chloride Balance

Findings and Interpretation. The chloride balances parallel closely those of the sodium, and the same interpretations are valid. There is generally more chloride than sodium in the urine and less chloride than sodium in the exudate. The exudate percentage of the chloride output is therefore lower than in the case of the sodium. The chloride losses in the exudate, however, are always in the same range as those of the sodium.

TABLE IX.—*Sodium, Potassium and Chloride Balances; Full-Thickness Burns; Fatal.*

Period		Sodium					Potassium					Chloride				
Dates		Intake	Output			Balance	Intake	Output			Balance	Intake	Output			Balance
(Inc.)	Days	Gm.	Urine Gm.	Exudate Gm.	Exudate %	Gm.	Gm.	Urine Gm.	Exudate Gm.	Exudate %	Gm.	Gm.	Urine Gm.	Exudate Gm.	Exudate %	Gm.
Pt. 268; female; age 83; per cent burn: 62% total; 22% full thickness; 10/28/45.																
10/28–11/2	5+	33.2	0.9	25.5	96.5	+ 6.8	6.0	9.0	0.0	0.0	−3.0	42.3	2.0	30.9	94.0	+ 9.4
11/3–11/10	8	9.0	0.6	15.4	96.0	− 7.0	12.6	11.8	2.2	15.7	−1.4	12.5	1.5	18.9	92.6	− 7.9
Pt. 262; male; age 64; per cent burn: 85% total; 58% full thickness; 9/6/45.																
													Urine and Feces			
9/6–9/9	3+	42.6	5.3	30.7	85.0	+ 6.6	3.2	8.5	1.0	10.5	−6.3	50.9	8.8	20.0	69.4	+22.1
9/10–9/13	4	19.7	0.3	36.8	99.0	−17.4	4.1	9.2	1.2	11.5	−6.3	14.6	2.1	24.0	92.0	−11.5

The reasons for the differences in the output distribution between urine and exudate of chloride as compared with sodium are various. Since the fluid lost on the burn surface is largely extracellular fluid, it is to be expected that there should be more sodium than chloride by equivalence. Extracellular fluid contains three parts of sodium (145 mEq/L) to two parts of chloride (100 mEq/L).* If sodium chloride solution is used as part of the fluid therapy, 30 per cent more chloride than sodium is given in terms of the normal distribution of these ions in the extracellular fluid and there is an excess of chloride ion to be excreted by the kidney.†

D. Potassium Balance

Findings and Interpretation. Potassium balances are available in nine patients (Tables VI-IX). In all eight of the extensively and deeply burned patients the balances were initially negative, 1 to 5 Gm. being lost per day for the first two to three

* To avoid giving a physiologic excess of chloride over sodium ion and to provide a small amount of potassium, several of these patients were offered a drink of isotonic sodium of both the chloride (60 per cent) and bicarbonate (40 per cent and flavored with a fruit juice containing potassium. Nausea prevented the extensively burned patients from drinking significant quantities of this concoction.

† There were instances in which there is a slightly disproportionate loss of chloride (Cases 268 and 269), and other instances (Case 262) in which there is a slightly greater loss of sodium in the exudate than of chloride. These minor differences in absolute quantity may be traceable to unpredictable alterations in the permeability of the burned tissue. When the cells of burned skin become permeable to extracellular ions[3] sodium appears to penetrate the cells somewhat faster and in larger quantities than chloride. For this reason there may be phases after a burn when some of the sodium which would otherwise appear in the dressing is lost into and retained in the burned cells of the skin.

days. In the four who survived and in one of those who succumbed, this negative potassium balance yielded to a positive one, persisting in the four who survived with little change up to discharge from the hospital. Thus the potassium balance is the reciprocal of the sodium. It also bears no apparent relation to the nitrogen balance, for those patients who came back into positive potassium balance did so in the first few days, whereas the positive nitrogen balance which followed the negative nitrogen balance did not appear for several days to weeks later.

Explanation of potassium balance balance may be sought in the therapeutic regimen, the red cell hemolysis, and expansion of the extracellular space, rather than in the "alarm reaction" and negative nitrogen balance. In relation to the therapeutic regimen it is pertinent that when a healthy normal adult is placed on an intake essentially free of potassium and partially fasted, he shows a strongly negative potassium balance for several days, before coming into stabilization at a slightly negative potassium balance. This early negative potassium balance is due to the continued excretion of dietary potassium ingested in the preceding days.[10] His zero (or slightly negative) potassium balance then persists during the phase of starvation in which fat is being metabolized, until muscle tissue begins to break down, at which time a strongly negative potassium balance again appears.

Immediately after the burn these severely burned patients were partially fasted, for they were able to take but little by mouth, and in the course of their calorically inadequate parenteral therapy very little potassium was administered. The only significant potassium given these patients was the small amount found in plasma (approximately 5 mEq/L) and the potassium in administered red blood cells. As described previously, this red cell potassium is not immediately available to the patient unless the red cells of the donor, or of the patient himself, are being hemolyzed. Since these extensively burned patients' own red cells were being hemolyzed[11] a small quantity of potassium was available to them from that source (see below). Thus the nature of the patients' treatment tended to produce a negative potassium balance in the first few days in the hospital and only as the patient began to take potassium by mouth, to eat fruit juices, meat and other potassium-containing foods, did he come into positive potassium balance.

The question remains whether or not the initial negative potassium balance represents a loss of potassium greater than one would predict merely by the continued excretion of previously ingested dietary potassium. In all nine of the patients in whom potassium balances are available it is seen that during the first few days in the hospital, when the patient is in negative potassium balance, the combined output of potassium by urine and feces is between 2 and 5 Gm. per day. In no patient is it larger than 5 Gm. per day and in most of them it is 3 or 4 Gm. per day. This amount of potassium (approximately 100 mEq.) is less potassium than the patient is found to excrete in his urine later on in his stay when he is in positive potassium balance and is

presumably building tissues. It is also not significantly more potassium than the average adult in balance excretes per day. It is, therefore, impossible to state on this evidence alone that the early negative potassium balance represents the ionic aspect of a cell-destroying catabolic phase. Although this potassium presumably comes from tissue cells, the loss of potassium amounts to scarcely more than 1 or 2 per cent of the total potassium in the body.[10]

The potassium balance cannot be regarded alone in the light of intake and output. The dietary intake does not represent the sole source of potassium, because potassium is released from red blood cells by hemolysis. Furthermore, the plasma potassium concentration is often slightly reduced in the early period. The potassium appearing in the urine does not represent the only "output" of potassium from cells, since the expansion of the extracellular space permits the accumulation of some additional extracellular potassium which is in a sense "output" because it is put out of cells into body fluids.

Therefore, it is possible to make a calculation in which "intake" includes hemolysis potassium as well as potassium from diet and plasma therapy, and "output" includes all the potassium appearing anew in the extracellular space (*i.e.*, in the wound, feces, urine, or in the expanded extracellular space itself). By this method a balance chart may be plotted which represents the balance of the body cell mass with the extracellular fluid. Though such a complicated calculation doubtless comes closer to telling us the facts than the simple intake-output balance, it has not in these cases changed the interpretation significantly because the new potassium appearing from hemolysis is approximately equal to the potassium stored away in the expanded extracellular space.

The *role of the exudate* in potassium loss is less significant than is the case with sodium. In the seven patients in whom potassium losses in the exudate were measured, the exudate potassium loss is 20 per cent or less of all the potassium lost from the body with the one exception of a patient (Case 234) who died, and in whom exudate potassium comprised 30 and 45 per cent of the potassium lost from the body in the two periods measured.

Were the sodium and potassium found in the exudate to arise solely from extracellular sources, one would expect approximately 18 times as much sodium as potassium to be found in the exudate on the basis of weight. The ratio is often this high or higher. In most of the exudates measured there is seven to 20 times as much sodium as potassium by weight. In two of the patients who died (Cases 262 and 268) there is almost 30 times as much sodium as potassium in the exudate. These wide variations in the sodium-potassium ratio in the exudate are again traceable presumably to unpredictable variations in the degree of intracellular loss or penetration. In a few patients, the order of magnitude is such that a little more potassium appears in the exudate than one would predict from the sodium loss. This may be due to the loss of potassium from tissues directly in or underneath the burn where cells are damaged and cell permeability is altered.[3]

The *sodium-potassium ratios* in the balances of the burned patient indicate

in general a reciprocity or antagonism. When the patient is in early positive sodium balance he is not infrequently in negative potassium balance and the converse may be true a few days later in his stay. This might be used as

TABLE X.—*Potassium:Nitrogen Ratios; Minor Burn.*

Period		Intake			Balance			Exudate		
Dates (Inc.)	Days	N Gm.	K mEq	K/N mEq/Gm.	N Gm.	K mEq	K/N mEq/Gm.	N Gm.	K mEq	K/N mEq/Gm.
Pt. 264; female; age 41; per cent burn: 5½% total; 0% full thickness; 10/8/45.										
10/8	1 –							0.5	1.28	−0.26
10/9	1	16.0	111	6.9	+2.8	+70	25.0	0.6	0.26	0.43
10/10	1	14.5	92	6.3	+0.2	+26	130.0	0.6	0.26	0.43
10/11	1	12.0	105	8.7	−4.3	+44		0.3	0.0	
10/12	1	17.5	120	6.9	+0.5	+54	108.0	0.0	0.0	
10/13	1	24.3	154	6.3	+5.2	+69	13.2	0.0	0.0	
10/14	1	24.3	148	6.1	+3.7	+56	15.1	0.0	0.0	
10/15	1	15.2	163	10.7	+4.2	+67	15.9	0.0	0.0	
10/16	1		133			+36		0.0	0.0	
10/9–10/15		123.8	1026	8.3	+12.3	+386	31.4	1.5	0.52	0.35

evidence to show that in the presence of this trauma potassium moves out of the cell and sodium passes into the cell. Though such events doubtless take place in the burned skin[3] we have no evidence that they are particularly widespread because, as pointed out above, the extent of potassium loss is not greater than one would predict from starvation alone. The positivity of the sodium balance is related to expansion in the sodium space of the body, only a fraction of which is intracellular, and to therapy which includes large amounts of sodium.

TABLE XI.—*Potassium:Nitrogen Ratios; Partial-Thickness Burn.*

Period		Intake			Balance			Exudate		
Dates (Inc.)	Days	N Gm.	K mEq	K/N mEq/Gm.	N Gm.	K mEq	K/N mEq/Gm.	N Gm.	K mEq	K/N mEq/Gm.
Pt. 254; male; age 38; per cent burn: 45% total; 5% full thickness; 5/29/45.										
5/29–6/1	3+	132.5	335	2.5	+67.1	−33.2		8.0	18.0	2.2
6/2–6/8	7	157.9	985	6.2	−89.3	−10.2	0.11	22.1	43.6	1.9
6/9–6/18	10	273.2	1585	5.8	−57.3	+197		22.7	61.3	2.7
6/19–6/28	10	305.5	2040	6.7	−13.7	+279		11.0	33.3	3.3
6/29–7/8	10	301.9	2430	8.1	+23.3	+64	2.7	9.0	0	
7/9–7/18	10	303.3	1850	6.1	−0.1	−120	1200	1.2	0	
7/19–7/28	10	307.3	2050	6.7	+105.7	+66.0	0.63	0	0	

E. Potassium-Nitrogen Ratios

Living tissue other than fat, skin and connective tissue tends to contain a constant ratio of nitrogen to potassium. This is true of skeletal and heart muscle, liver, and certain other parenchymatous tissues. Skeletal muscle comprises the largest homogeneous mass of tissue in which the ratio potassium: nitrogen is constant. This constancy arises from the histochemical structure of these tissues. There are 2.5 to 3.5 mEq. of potassium per gram of nitrogen in these tissues.[12]

It therefore becomes of interest to relate our potassium and nitrogen data to discover whether or not the two are moving together in this ratio. In Tables X to XIII are shown potassium:nitrogen ratios for nine patients. In two of these patients exudate data are not available.

The potassium:nitrogen ratio of the balances may be influenced by the nature of the intake as well as by the nature of the metabolic processes in the patient. The intake potassium:nitrogen ratio must therefore be considered when interpreting the potassium:nitrogen ratio of the balance. If a patient's

TABLE XII.—*Potassium:Nitrogen Ratios; Full-Thickness Burns; Survival.*

Period		Intake			Balance			Exudate		
Dates (Inc.)	Days	N Gm.	K mEq	K/N mEq/Gm.	N Gm.	K mEq	K/N mEq/Gm.	N Gm.	K mEq	K/N mEq/Gm.
Pt. 210; female; age 34; per cent burn: 31% total; 25% full thickness; 12/28/44.										
12/28–12/31	3+	64.0	64.0	1.0	+25.7	−174				
1/1–1/7	7	223.1	885	3.9	+20.2	+330	16.3			
1/8–1/17	10	332.7	1710	5.1	−34.3	+220				
1/18–1/27	10	189.5	1170	6.2	−83.4	+102				
1/28–2/6	10	132.0	1010	7.6	−24.0	+172				
2/7–2/16	10	154.9	1080	7.0	−3.3	+265				
2/17–2/26	10	128.3	1140	8.9	+12.6	+346	27.5			
2/27–3/8	10	166.4	1180	7.1	+53.6	+460	8.6			
3/9–3/18	10	130.5			+27.0					
3/19–3/28	10	99.5	951	9.6	+29.5	+292	9.9			
3/29–4/7	10	145.8	1100	7.5	+34.6	+266	7.7			
4/8–4/17	10	122.9			+28.0					
4/18–4/27	10	129.8	1095	8.4	+64.6	+473	7.3			
4/28–5/4	7	107.1			+52.1					
Pt. 217; female; age 26; per cent burn: 78% total; 45% full thickness; 1/12/45.										
1/12–1/15	3+	127.5	181.0	1.4	+52.6	−138				
1/16–1/22	7	260.2	1200	4.5	+ 4.3	+305	70.7			
1/23–2/1	10	306.5	1880.0	6.1	−74.6	+341				
2/2–2/11	10	327.0	1940.0	5.9	−18.6	+635				
2/12–2/21	10	372.7	1620.0	4.3	+79.5	+615	7.7			
Pt. 260; female; age 27; per cent burn: 28% total; 12% full thickness; 8/13/45.										
8/13–8/16	3+	47.8	125	2.6	+28.4	−53.7		5.3	38.3	7.2
8/17–8/23	7	213.8	1020	4.8	+95.8			23.7	102	4.3
8/24–9/2	10	280.8	1670	5.9	+46.2	+107	2.3	25.9	120	4.6
9/3–9/10	8	203.1	1410	6.9	+12.0	+190	15.8	25.3	0.0	
Pt. 269; male; age 60; per cent burn: 27% total; 20% full thickness; 11/2/45.										
11/2–11/6	4+	90.5	188	2.1	− 7.1	−200	28.2	23.6	51.2	2.2
11/7–11/12	6	120.7	680	5.7	−33.0	+136		16.4	92.0	5.6
11/13–11/23	11	305.4	1690	5.5	−29.8	+530		38.0	222.0	5.9

food consists largely of meat and other animal protein the potassium:nitrogen ratio of the intake will tend to be the same as the potassium:nitrogen ratio of the patient's own tissues. However, certain fruits and vegetables contain more potassium per unit nitrogen than is found in meat and for this reason we find the potassium:nitrogen ratios in the intake of these patients running in the neighborhood of 5 to 9 mEq. potassium per gram nitrogen, the average for the whole group being approximately 7. In the first few days after the burn the potassium:nitrogen ratio is significantly less because the intake of potassium is virtually entirely that found in plasma and is far outweighed by the protein

content thereof (the potassium:nitrogen ratio of plasma being approximately .077 mEq. per gram).

The potassium:nitrogen ratios of the balance can only be calculated when the balances of both potassium and nitrogen are in the same direction. If the patient is in positive nitrogen balance and negative potassium balance or vice versa the calculation of the potassium:nitrogen ratio has little significance. Furthermore, if either of these balances approaches zero, for example a negative potassium balance of .04 or .03 Gm., the ratio becomes a very high or very low figure and has little significance. An example of this is to be found in the fifth period of a patient (Case 254) where a potassium:nitrogen ratio of 1200 is observed due to a fractional nitrogen balance.

In general the potassium:nitrogen ratios of the balances are extremely variable but tend to run from 7.0 to 20.0, again indicating a turnover of potassium disproportionately high to that of protein or nitrogen.

TABLE XIII.—*Potassium:Nitrogen Ratios; Full-Thickness Burns; Fatal.*

Period		Intake			Balance			Exudate		
Dates (Inc.)	Days	N Gm.	K mEq	K/N mEq/Gm.	N Gm.	K mEq	K/N mEq/Gm.	N Gm.	K mEq	K/N mEq/Gm.
Pt. 268; female; age 83; per cent burn: 62% total; 22% full thickness; 10/28/45.										
10/28–11/2	5+	96.9	154	1.6	+19.4	−77		24.1	0.0	
11/3–11/10	8	100.0	324	3.2	− 2.0	−36	18.0	17.0	56.2	3.3
Pt. 262; male; age 64; per cent burn: 85% total; 58% full thickness; 9/6/45.										
9/6–9/9	3+	105.6	82.0	0.8	+55.0	−162		20.3	25.5	1.25
9/10–9/13	4	61.1	105.0	1.7	−28.5	−162	5.7	21.7	30.6	1.41
Pt. 234; male; age 68; per cent burn: 55% total; 45% full thickness; 3/8/45.										
3/8–3/11	3+	142.3	230	1.6	+78.0	−187		19.6	126	6.4
3/12–3/17	6	131.8	690	5.3	−26.4	+67		25.1	276	11.0

The *potassium:nitrogen ratios of the exudate* in four cases (254, 260, 268 and 269) averaged between 2.0 and 5.0, a figure which one would predict were the potassium and nitrogen to arise largely from intracellular sources. We have already seen in examining the data for sodium and potassium in the exudate that there is often more potassium present than one would predict from the sodium content—interpreted as meaning that some of the potassium comes from cells rather than from extracellular fluid. This finding of exudate potassium:nitrogen ratios near that found in tissue, and nearer the tissue ratios than either the intake or the balance ratios, may corroborate the concept that much of the exudate's solute arises from cells. When the exudate is purulent much of the potassium and nitrogen is present *in the exudate* in intracellular form, in white cells and bacteria, and thus an "intracellular" potassium:nitrogen ratio is produced regardless of the potassium source.

In two extensively and fatally burned patients (Cases 262 and 234) the potassium:nitrogen ratios in the exudate range from 1.25 to 11.

In summary, the potassium:nitrogen ratios in these patients have not been consistent; the intakes are high in potassium relative to nitrogen (as compared with tissue composition), the balances are extremely variable; as a

general rule the exudate tends to lose the two substances in approximately the ratio they are found in cellular tissues.

SUMMARY

1. Balances of nitrogen, sodium, potassium and chloride have been measured in lightly and severely burned patients.

2. Exudate loss of these substances has been measured by analysis of dressings and beddings; these measurements, though time-consuming, are of fundamental importance to any evaluation of the metabolic state of burned human beings.

3. The balance, the role of the exudate loss, and the interrelationships of nitrogen, sodium potassium and chloride metabolism in such patients have been discussed and interpreted in the light of the above findings.

4. The nitrogen balance in the severely burned patient, initially positive during the period of plasma therapy, later becomes negative and remains so until convalescence is well advanced. The exudate nitrogen may constitute 25 to 30 per cent of total nitrogen losses during the period of maximum wound slough and purulent discharge.

5. The sodium balance, initially positive during the period of wound expansion and electrolyte therapy, becomes negative during resorption of wound edema and diuresis. The exudate sodium may comprise 95 per cent (or more) of all sodium losses, with concomitant urinary sodium losses reduced virtually to zero.

6. The chloride balance resembles that of sodium with the exception that the urinary loss may be higher and exudate loss lower.

7. A negative potassium balance of 2 to 5 Gm. daily is the rule for the initial two to three days. Positive balance is promptly attained as oral potassium intake is recommenced. There is little correlation between nitrogen and potassium balance, since positive potassium balance is regained several days to weeks prior to positive nitrogen balance. Exudate potassium comprises at a maximum but 20 per cent of the total potassium loss.

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POTASSIUM DEFICIENCY IN SURGICAL PATIENTS*

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THE IMPORTANCE of considering the replacement of intracellular electrolytes in parenteral fluid therapy has been emphasized in many types of electrolyte problems in recent years.[1-8] The ability to measure serum potassium levels quickly by means of the flame photometer[9] and knowledge of the electrocardiographic alterations associated with hypopotassemia[10, 11] have furnished the clinician useful tools with which to determine the need in a given patient for replacement solutions containing potassium. The present study involved, first, the determination of the prevalence and of the degree of hypopotassemia present in routine preoperative and postoperative surgical patients in whom fluid balance is one of the major therapeutic problems. Second, an attempt was made to replace potassium where specific indications arose as indicated by serum potassium levels and electrocardiographic alterations.

METHOD OF STUDY

Several surgical patients who presented various types of electrolyte problems were studied. These patients were treated parenterally with solutions containing sodium chloride, glucose, ammonium chloride, Ringer's lactate solution, one-sixth Molar sodium lactate, amigen, plasma, or blood, with no other source of potassium. On more than 25 patients many serum potassium levels were determined, using the flame photometer,[9] and electrocardiograms were taken. All of these patients had, as a unifying factor, a serum potassium level below 4.25 milliequivalents per liter (17 mg. per 100 cc.) sometime during the course of study. In this paper it is assumed that in the cases studied, a low serum potassium level was associated with a cellular deficit of potassium.[1, 12]

RESULTS

It was decided to present data on 11 cases carefully studied. Table I summarizes the pertinent clinical and biochemical data on these patients. The patients were all adults with diverse common types of surgical conditions. From a chemical viewpoint, the patients may be divided into: (1) those with alkalosis; (2) those with a normal acid-base balance; and (3) one with acidosis. The alkalosis of these patients was caused by vomiting, frequent gastric aspirations, and/or prolonged Wangensteen drainage of the upper gastro-intestinal tract, with loss of chlorides in excess of sodium from the extracellular fluid. R. P. was a patient with uncompensated alkalosis and hypopotassemia, as has been described in Cushing's Syndrome.[13, 14] One patient with mild diabetic acidosis, M. H., was included in this table.

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TABLE I.—*Clinical and Biochemical Data of Eleven Surgical Patients with Hypopotassemic.*

Patient	Surgical Condition	Wangensteen Drainage	Serum*		Daily Urine Output	Lowest** Serum K Observed	No. of Low‡ Serum K Levels	E.K.G. Changes	Urea N†	Course
		cc.	HCO_3 meq./L.	Cl	cc.	meq./L.			mg. %	
I.H., 70 Male	Ca of rectum. Abdominal-perineal resection. Evisceration. Peritonitis	1000–2500 q.d.	HCO_3 50	Cl 88	950–1500	2.6	7	+	52.0	KCl given parenterally and orally in large amounts. Survived 2 additional operations.
S.F., 63	Pyloric obstruction. Duodenal ulcer. Preoperative	1000–3500 q.d.	HCO_3 52	Cl 77 pH 7.6	1000–1500	2.75	9	+	35.8	Postoperatively, KCl given orally. Recovery was prolonged.
M.C., 60 Female	Ca of stomach. Gastro-jejunostomy. Post operative obstruction	1000–2000 q.d. by aspiration	HCO_3 39	Cl 88	600–1100	2.9	8	+	Normal	Small amounts of KCl given orally. Low serum K level on discharge.
G.S., 72 Female	Ca of jejunum. Resection with end-to-end anastomosis. Postoperative obstruction.	1000–3000 q.d. by aspiration	HCO_3 36	Cl 90	600–1000	2.8	2	+	34.0	No KCl given. Died 5 days postoperatively from perforation of suture line with peritonitis.
R.P., 33 Female	Cushing's Syndrome. Unilateral adrenalectomy. Postoperative	Frequent vomiting q.d.	HCO_3 31	Cl 90 pH 7.5	900–3000	2.9	6	+	Normal	KCl given by clysis and orally. Recovery.
E.B., 19 Female	Partial intestinal obstruction. Preoperative.	800–1200 q.d.	Normal		800–1300	3.7	3	+	Normal	No KCl given. Recovery.
J.C., 79 Female	Mesenteric thrombosis. Resection with end-to-end anastomosis. Postoperative	250–1500 q.d.	HCO_3 33	Cl 91	500–1400	2.5	4	+	34.0	Parenteral and oral KCl given in large amounts. Recovery.
A.W., 60 Female	Ca of ileum and colon. Resection with ileo-colostomy. Postoperative	1000–2000 q.d.	Normal		1000–1500	4.0	2	+	Normal	No KCl given. Recovery.
M.H., 35 Female	Recurrent Ca of colon with intestinal obstruction	250–1500 q.d.	HCO_3 38	Cl 90	800–2500	3.0	6	+	Normal	Treated non-operatively. Parenteral and oral KCl given in large amounts. Recovery.
J.G., 34 Female	Pernicious vomiting of pregnancy Second trimester	Frequent vomiting for 2 weeks	HCO_3 35	Cl 92 pH 7.5	500–1400	3.1	2	+	Normal	24 Gm. KCl given orally in three days. Recovery.
M.H., 53 Female	Diebetic acidosis. Cholelithiasis	Vomited two times before admission	HCO_3 22	Cl 66	900–1500	3.5	1	+	Normal	KCl given parenterally Recovery.

* Values recorded in this chart represent highest serum HCO_3 and lowest serum Cl observed during period of study.

** Low normal serum K = 4.25 meq./L. (17 mg. %).

† Highest urea N observed at the same time a low serum potassium was present.

‡ Includes entire period of study.

The role of alkalosis in accentuating intra-cellular potassium loss may be shown in the study:

Case 1.—S. F. was a 63-year-old male with a scarred duodenal ulcer, resulting in severe pyloric obstruction. The patient had been vomiting for three days prior to his admission on the medical service. On admission, March 17, 1949, the serum HCO_3 was 52.3 meq./L., serum Cl = 77. meq./L., pH = 7.6; serum Na = 137. meq./L., serum K = 4.75 meq./L., blood urea N = 31. mg. per 100 cc. He was treated with blood, saline, and glucose solutions parenterally, and frequent gastric aspirations were performed. This therapy resulted in partial correction of his severe alkalosis. March 24, 1949, the pylorus became completely obstructed with the loss of over four liters of highly acid gastric juice. He was transferred to the surgical service, at which time a Levin tube was passed and continuous Wangensteen drainage instituted. At this time, March 25, 1949, the serum HCO_3 was 50.2 meq./L., serum Cl = 85. meq./L., serum Na = 137. meq./L., serum K = 4.3 meq./L., and blood urea N = 42.2 mg. per 100 cc. (Table II).

Electrolyte and fluid balance data on this patient are presented in Table III. Several aspects of this study are of interest. First, the major loss of potassium, in this case of

TABLE II.—*Blood Chemical Determinations in S. F. Case of severe alkalosis due to pyloric obstruction with profuse vomiting. Operation occurred on March 28, 1949.*

Date	Time	Blood Urea N mg %	Serum HCO_3 meq./L	Serum Cl meq./L	Serum Na meq./L	Serum K meq./L
3/25	9 am	42.2	50.2	85.0	137.0	4.3
3/26	9 am	36.8	45.5	89.0	139.0	3.4
	6 pm	....	38.3	....	141.5	3.1
3/27	12 N	32.2	37.4	96.0	137.0	3.2
	7 pm	....	32.0	....	139.0	2.8
3/28	7 am	24.1	27.0	102.0	140.0	2.75

alkalosis associated with pyloric obstruction, occurred in the urine and not in the gastric juice. Second, potassium migrated out of the cells and was lost in the urine and gastric juice in excess of the K:N ratio of 2.4 meq. K:1 Gm. N.[6] As the alkalosis was corrected, the urinary loss of potassium diminished and tended to approach the K:N ratio of 2.4. This observation is what one might expect in view of Darrow's recent work on rats, demonstrating the high degree of correlation between the concentration of serum bicarbonate and the composition of muscle with respect to total potassium and intracellular sodium.[15, 16] Third, ammonium chloride and sodium chloride corrected the alkalosis but had no effect on the potassium deficiency, other than to decrease the urinary excretion of potassium by lowering the serum bicarbonate, thus slowing down the transfer of potassium from the cells into the extracellular fluid. Fourth, despite one liter of blood and two liters of a modified Ringer's solution, the serum potassium level decreased during the period of study, indicating the inadequacy of Ringer's solution and of blood in replacing the existing potassium deficiency (Table II).

The patient was operated upon within one hour after completion of the study, and a subtotal gastrectomy and gastro-jejunostomy was performed. Postoperatively he developed gastric retention and was quite ill for three weeks. During this time, sufficient food and small oral doses of potassium chloride were fed to the patient to replace most of his potassium deficiency. Two and one-half weeks were required for his serum potassium level and electrocardiogram to return to normal (Fig. 1).

That potassium deficiency may develop in the presence of a normal acid-base balance may be seen in the following case.

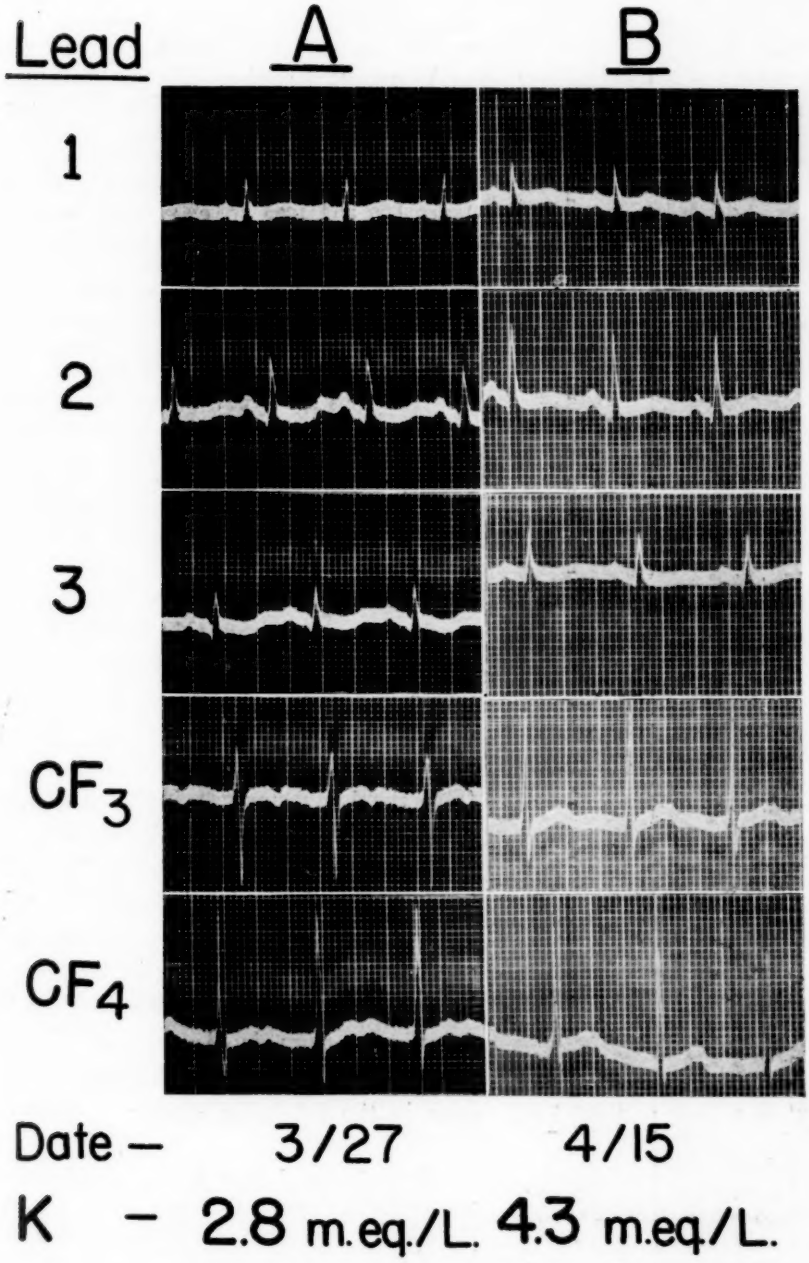

FIG. 1.—S. F., age 63, presented the problem of severe alkalosis, associated with vomiting due to complete pyloric obstruction. (A) On March 27, EKG shows lengthening of Q-T intervals and flattened T-waves. Serum K was 2.8 meq./L. (B) On April 15, over two weeks postoperatively, EKG shows a more normal appearing pattern. Serum K was 4.3 meq./L.

TABLE III.—*External Exchanges of Water, Electrolytes, and Nitrogen in S. F.*‡

Period Dates	Intake*							Output									Balance			
									Urine				G-I Fluid**							
	H_2O	Cl	Na	K†	NH_4	N††	Blood	CHO	Vol.	Cl	Na	K	N	Vol.	Cl	Na	K	N	Cl	Na	K	N	K/N
	cc.	meq.	meq.	meq.	meq.	grams	cc.	grams	cc.	meq.	meq.	meq.	grams	cc.	meq.	meq	meq.	grams	meq.	meq.	meq.	grams	
3/25–26	4300	450	280	1.4	170	2.4	500	165	1100	6.4	37	67	8.5	2500	280	60	17	2.	+163	+183	−82.6	−8.1	10
3/26–27	3200	510	340	2.3	170	2.4	0	110	1620	16.	55	53	14.0	1400	250	62	9	1.4	+244	+223	−59.7	−13.0	4.3
3/27–28	3350	457	287	3.7	170	2.4	500	117	1670	31.5	42	36	16.0	1540	287	69	11	1.6	+138	+176	−43.3	−15.2	2.7

* Entire intake given in form of intravenous fluids.

** No fluid lost by rectum during this entire study.

† Includes 1.4 meq. of K contained in serum of 500 cc. of whole blood, assuming H + = 45, and K contained in one liter of modified Ringer's solution.

†† Does not include N contained in 500 cc. of whole blood.

‡ Weight = 72 Kg.

Case 2.—E. B., a 19-year-old white female, was admitted to the surgical service with the diagnosis of partial intestinal obstruction. A Cantor tube was passed on admission and was attached to Wangensteen suction. She was maintained on two liters of amigen and one liter of five per cent glucose-in-saline for six days preoperatively. For four of these days, potassium balance studies were performed (Table IV). During this period between 800 and 1200 cc. of intestinal juice a day were drained off, with a corresponding loss of from 5. to 8. meq. of potassium. Her daily urine output was maintained at 800 to 1300 cc., with a loss of from 18. to 30. meq. of potassium a day. Her serum potassium level dropped to 3.7 meq./L. during the course of study (Table V) and remained at this level until the postoperative period, at which time she was able to ingest sufficient potassium in her diet to replace her existing potassium deficiency and restore her serum potassium level to normal. Minor electrocardiographic alterations occurred and are shown in Fig. 2.

This case is presented as typical of many cases on surgical wards, in which, with (1) prolonged Wangensteen drainage of the upper gastro-intestinal tract, (2) potassium deficient intravenous fluids, (3) good urinary output, potassium is gradually drained from the body stores, with progressive increase in the weakness of the patient.

During intestinal obstruction, loss of potassium into the gastro-intestinal tract may be considerable. Falconer observed the concentration of potassium in vomitus may be five times that in the serum.[17, 18] That severe potassium deficiency may develop in a patient with intestinal obstruction can be seen in the following study:

Case 3.—J. C. was a 79-year-old white female, who presented the problem of mesenteric thrombosis. Previous to admission, profuse vomiting of coffee-ground material had occurred. Operation on April 12, 1949, revealed two liters of blood-tinged fluid in the peritoneal cavity. Five feet of gangrenous bowel containing over one and one-half liters of sero-sanguinous fluid were found. This bowel was resected and an end-to-end anastomosis was performed. A Levin tube was

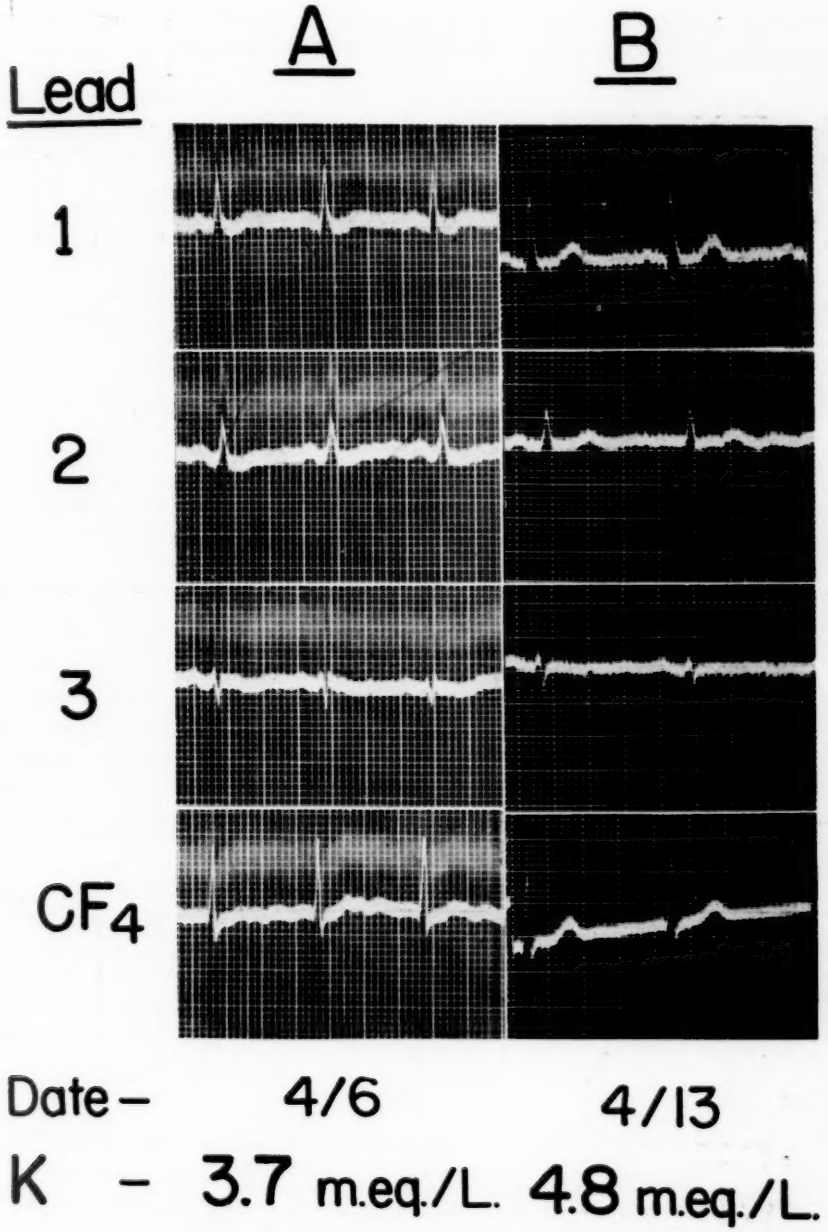

FIG. 2.—E. B., age 19, was kept on prolonged Wangensteen drainage of the small intestine for six days preoperatively. (A) On April 6, EKG shows the lengthening of Q-T intervals and depression of the T-waves. Serum K was 3.7 meq./L. (B) On April 13, postoperatively, EKG appears more normal. Serum K was 4.8 meq./L.

passed and continuous Wangensteen suction was started. The patient received one liter of blood and two liters of amigen immediately postoperatively. In the morning, April 13, 1949, the blood urea N was 24.4 mg. per 100 cc. serum HCO_3 = 33. meq./L., serum Cl=91 meq./L., serum K=4.2 meq./L. In the next two days the patient

TABLE IV.—*External Exchanges of Water and Potassium in E. B.*‡

Period	Intake*		Output				Balance
			Urine		G-I Fluid**		
Dates	H_2O	K†	Vol.	K	Vol.	K	K
	cc.	meq.	cc.	meq.	cc.	meq.	meq.
4/2–3	3000	5.0	800	26.0	1200	8.0	−29
4/3–4	3000	5.0	1160	30.0	950	6.0	−31
4/4–5	3000	5.0	1300	24.0	800	6.0	−25
4/5–6	3000	5.0	1050	18.0	900	5.0	−18

* Entire intake given in form of intravenous fluids.
** No fluid lost by rectum during this entire study.
† Two liters of 5 per cent amigen contains 5 meq. of K, by our own analysis.
‡ Weight =58 Kg.

TABLE V.—*Blood Chemical Determinations in E. B. Case of partial intestinal obstruction with preoperative preparation by Wangensteen drainage of small bowel for six days. Operation occurred on April 6, 1949.*

Date	Blood Urea N	HCO_3	Serum Cl	K
	mg. %	meq./L.	meq./L.	meq./L.
4–2	18.4	29.2	98	4.4
4–4	16.2	28.4	100	3.9
4–6	11.0	27.0	105	3.7
4–8	17.0	27.9	102	3.9
4–11	14.9	28.3	99	4.1
4–13	12.0	....	...	4.8

TABLE VI.—*External Exchanges of Water, Potassium, and Nitrogen in J. C.*‡

Period	Intake*				Output						Balance	
					Urine			G-I Fluid**				
Dates	H_2O	K†	N††	Blood	Vol.	K	N	Vol.	K	N	K	N
	cc.	meq.	Gm.	cc.	cc.	meq.	Gm.	cc.	meq.	Gm.	meq.	Gm.
4/16–17	4000	17.8	9.6	500	1120	25.0	16.0	2300	13.8	1.8	−21.0	−8.2
4/17–18	3500	18.4	12.0	0	900	18.0	16.3	1200	8.4	1.1	− 8.0	−5.4
4/18–19	3500	19.8	12.0	500	1400	28.0	18.5	250	2.0	...	−10.2	−6.5
4/19–20	2600	4.0	11.0	0	950	17.4	15.1	....	....	...	−13.4	−4.1

* Fluid intake given in form of intravenous fluids for first three days of study. Sips of fluid allowed on fourth day.
** Does not include K and N lost in enema fluid on April 17 and April 19.
† Includes K in amigen, serum of 500 cc. whole blood, and KCl given intravenously.
†† Does not include N contained in 500 cc. whole blood.
‡ Weight =48 Kg.

was gradually hydrated with potassium deficient parenteral fluids. On April 15, 1949, an electrocardiogram was first taken and revealed a pattern suggestive of hypopotassemia. Potassium chloride was started cautiously by vein, one gram being given slowly each day. Balance studies were begun on April 15, 1949, and carried through to April 20 (Table

VI). Clinically, the patient passed flatus two days postoperatively, the operation apparently being successful. However, the patient remained very weak and seemed exhausted throughout the postoperative period. On April 19, no potassium chloride was given to the patient to ascertain whether there would be any effect on the clinical course. On April 20, the patient was still weak and minimal ankle edema was observed. Slight dyspnea was present. Scattered moist râles were heard at the lung bases posteriorly. The heart sounds were of poor quality and a faint apical systolic murmur was present. The pulse was

TABLE VII.—*Blood Chemical Determinations in J. C. Case of mesenteric thrombosis observed postoperatively.*

Date	Blood Urea N	HCO_3	Serum Cl	K
	mg. %	meq./L.	meq./L.	meq./L.
4–13	24.4	33.0	91	4.2
4–15	34.0	29.3	94	3.5
4–16	37.0	27.5	99	...
4–18	14.0	30.0	101	2.9
4–20	16.0	32.0	96	2.5
4–22	8.3	30.0	101	5.1

regular and full. An electrocardiogram again revealed a tracing suggestive of hypopotassemia (Fig. 3). The serum potassium level at this time was 2.5 meq./L. (Table VII). Potassium chloride was started immediately by mouth, and in the next two days, the patient received approximately 325 meq. of potassium, including the potassium contained in the diet. On April 21, the patient seemed stronger. The ankle edema had disappeared. The lungs were clear to percussion and auscultation. Heart sounds were of better quality. A diuresis of fluid was observed in the next few days (Table VIII). On April 22, the serum potassium level was 5.1 meq./L., and the electrocardiogram appeared more normal

TABLE VIII.—*Illustrating Diuresis Occurring in J. C. Following the Administration of Large Doses of Potassium Chloride Orally.*

Period	Fluid Intake	Oral K Intake	Urine Vol.	Urine K Output
	cc.	meq.	cc.	meq.
4/20–21	2300	150	900	24
4/21–22	2900	175	3000	42
4/22–23	2050	50	2600	51
4/23–24	2250	50	2200	45

(Fig. 3). By this time, the patient was taking her diet quite well, and progressive improvement occurred. She was discharged on April 26, 1949.

This case is presented as one of intestinal obstruction in which progressive hypopotassemia developed in the postoperative period. This was inadequately combatted by potassium deficient parenteral fluids, as shown by the negative potassium balance (Table VI) and a drop in serum potassium levels (Table VII), occurring during the course of treatment. Withholding potassium for one day resulted in a drop of the serum potassium level to 2.5 meq./L. on April 20. It is not wise to attribute the development of this patient's mild congestive failure on that day solely to hypopotassemia. However, it may have been a contributing factor in an aged heart already rendered inefficient by

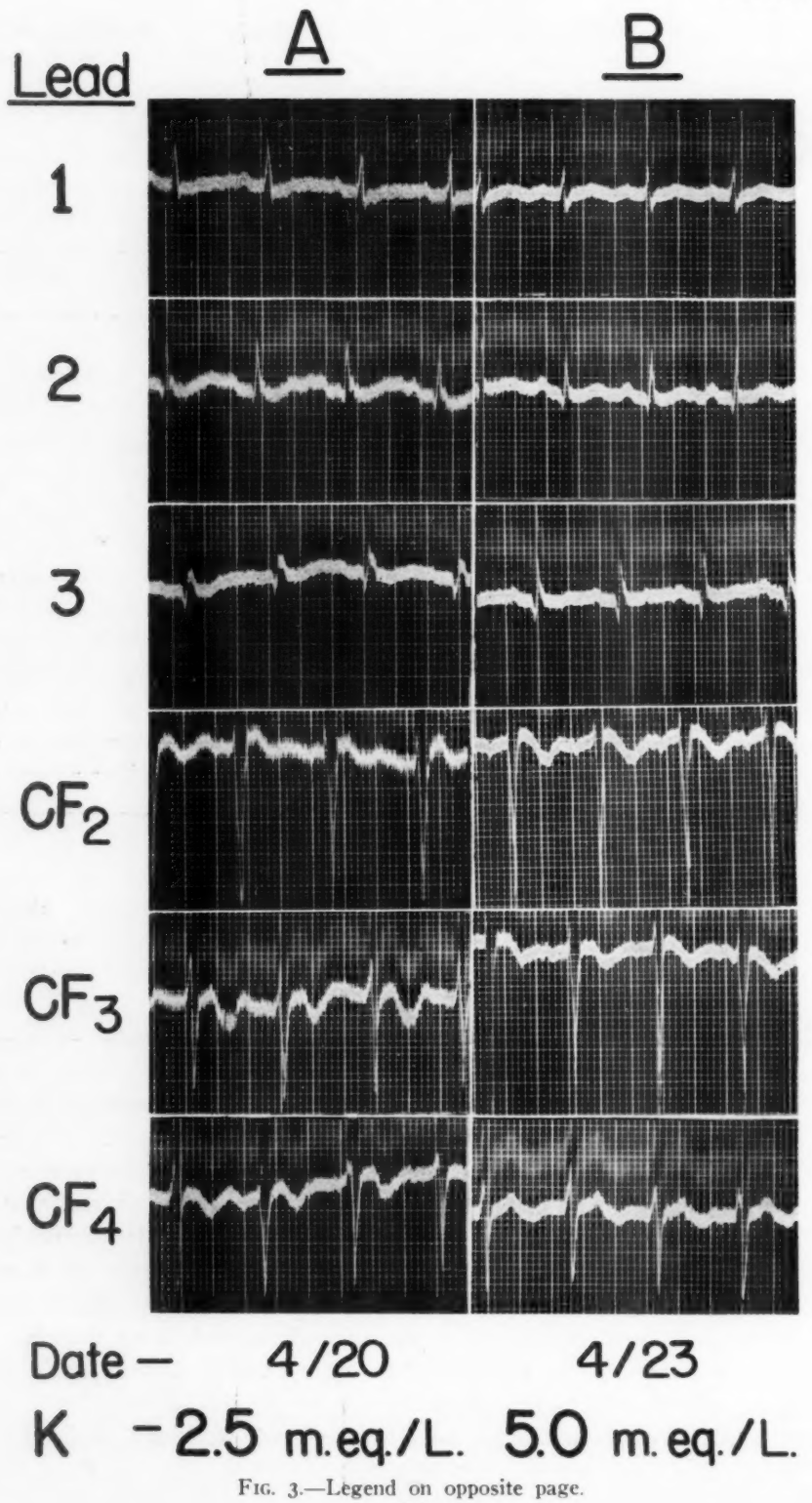

FIG. 3.—Legend on opposite page.

diseased coronary arteries. The good clinical response, electrocardiographic alterations, and diuresis occurring following the administration of large doses of potassium chloride orally is suggestive but not conclusive proof of this possibility.

DISCUSSION

Physiologic Aspects. In recent years, the quantitative movement of intracellular potassium into the extracellular fluid has been extensively investigated. For many years, release of potassium from the cell has been known to occur during cellular catabolism. In the past decade, potassium has been shown to move out of the cell in glycolysis,[19, 20] hemorrhage,[21, 22] shock,[23] dehydration,[24] alkalosis,[16] and whenever the excretion of potassium is greater than the intake.[15] This last fact is of prime importance when dealing with surgical patients maintained solely on parenteral fluids deficient in potassium. Excretion of potassium in excess of nitrogen and negative potassium balance have been observed in various groups of patients maintained on the usual types of parenteral fluids and may be accelerated postoperatively as part of an injury reaction.[25-28] In the production of a marked potassium deficiency in surgical patients, the importance of the continued renal excretion of potassium in the presence of hypopotassemia has been well-emphasized by Tarail and Elkinton.[12] In their patients, the concentration of potassium was never lower in the urine than in the serum. From our own observations on ten surgical patients studied during the period of hypopotassemia, we agree with this observation. Apparently, the renal tubules have a minimal rate of excretion of potassium and will not reabsorb potassium against a concentration gradient.[12] In fact, under certain conditions, experiments have shown that the renal tubules may secrete potassium.[29, 30]

Clinical Aspects. The clinical recognition of potassium deficiency depends primarily on the knowledge of conditions under which potassium loss occurs. The prevalence of these conditions in surgical patients has been emphasized in this paper. Clinical signs and symptoms are not common. However, electrocardiographic alterations are rather frequent in association with hypopotassemia. The characteristic electrocardiographic alterations of hypopotassemia, namely lengthening of the Q-T interval, depression of the S-T segment, lowering in the amplitude of the T waves, inverted T waves and frequent U waves, have been adequately described.[10, 11] We have found that the precordial leads, CF2, CF3, and CF4, are of particular value in detecting early changes. It is helpful to have a preoperative electrocardiogram on all surgical patients who are to undergo major surgery. During this study, parenteral potassium therapy

FIG. 3.—J. C., age 79, was observed during the postoperative phase, following resection of small bowel, which was gangrenous due to a mesenteric artery thrombosis. (A) On April 20, EKG shows the lengthening of Q-T intervals, flattened and inverted T-waves, especially in CF-4. Serum K was 2.5 meq./L. (B) On April 23, after 375 milliequivalents of potassium had been given by mouth, a more normal appearing EKG is seen. However, the T-waves in CF-2, CF-3 are still inverted. Serum K was 5.0 meq./L.

was often started on the basis of the clinical picture and electrocardiographic alterations, without waiting for the results of serum potassium levels to return from the chemical laboratory.

The question arises as to whether it is necessary to give supplementary potassium to all surgical patients maintained solely on intravenous fluids. To this one may make the obvious comment that in the absence of exogenous

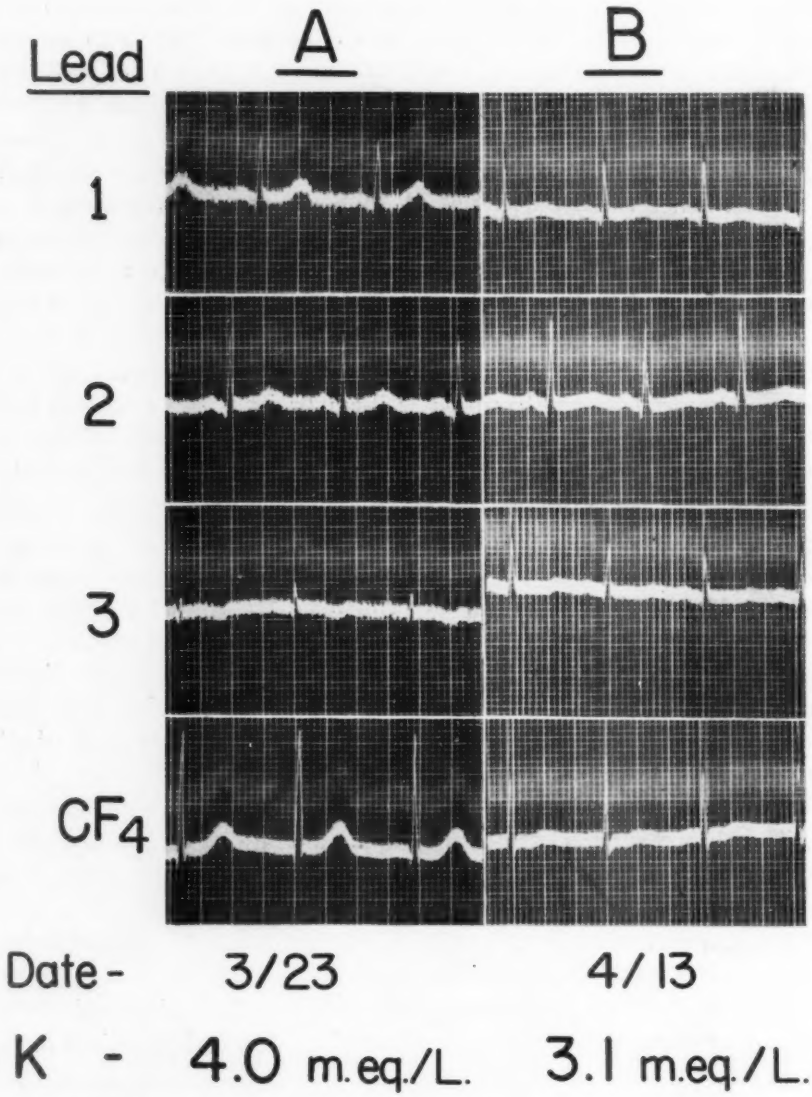

FIG. 4.—M. C., age 60, presented a far-advanced case of carcinoma of the stomach, with postoperative obstruction. (A) On March 23, EKG shows Q-T intervals at the upper limits of normal. Serum K was 4.0 meq./L. (B) On April 13, following three weeks of potassium deficient parenteral therapy, EKG shows prolonged Q-T intervals and flattened T-waves in all leads. Serum K was 3.1 meq./L.

potassium, potassium deficiency will always develop in these patients and will not be corrected unless potassium is supplied. That such a condition can exist on surgical wards is exemplified by M. C., who presented a terminal case of inoperable carcinoma of the stomach, in whom a gastro-jejunostomy was performed in an attempt to relieve obstructive symptoms. Unfortunately, these symptoms recurred soon in the postoperative period, and oral intake of food was correspondingly curtailed. She was maintained on a potassium deficient parenteral regimen, and, in turn, she maintained a low serum potassium level for her remaining three weeks' stay. She was finally discharged on the insistent request of her relatives, at which time she had a serum potassium level of 3.1 meq./L. with marked electrocardiographic alterations (Fig. 4).

It is of interest to mention the experimental results that have been obtained on rats placed on potassium deficient diets. Several investigators have demonstrated the development of focal necrosis throughout the myocardium with ultimate replacement of this heart muscle by connective tissue in rats kept on a diet extremely deficient in potassium.[31-33] Apparently, in the living organism the heart is one organ that is particularly susceptible to the harmful effects of prolonged potassium deficiency.

Therapeutic Implications. It seems logical to assume that the best way to treat potassium deficiency in surgical patients is to prevent any marked degree of potassium depletion from occurring, wherever possible. In our patients studied during the period of hypopotassemia, it was found that from 15 to 36 meq. of potassium was excreted in the urine daily. In the presence of severe alkalosis, one patient, S. F., already markedly depleted of potassium, excreted 67 meq. of potassium in the urine in a 24-hour period, in addition to 17 meq. of potassium which was lost in the Wangensteen drainage in the same period. From these observations, several types of potassium-containing solutions have been prepared and used by our surgical staff in recent months:

Solution I:	Sodium chloride	8.5 Gm.
	Potassium chloride	2.0 Gm.
	Glucose	50.0 Gm.
	Distilled water q.s. ad	1000.0 cc.

Use 1 to 3 liters per day for ℞ of moderate alkalosis or for routine daily maintenance of patients on prolonged Wangensteen drainage of the upper gastro-intestinal tract.

Solution II:	Sodium chloride	8.5 Gm.
	Ammonium chloride	8.5 Gm.
	Potassium chloride	2.0 Gm.
	Distilled water q.s. ad	1000.0 cc.

Use 2 to 3 liters per day for ℞ of severe alkalosis.

Solution III:	Sodium chloride	3.0 Gm.
	Ammonium chloride	4.5 Gm.
	Potassium chloride	2.0 Gm.
	Distilled water q.s. ad	1000.0 cc.

Use 1 to 2 liters per day for ℞ of moderate alkalosis. This is especially useful in cardiac patients with alkalosis in whom one does not wish to replace an excess of sodium.

In several of our cases of alkalosis, slightly low serum calcium values were occasionally observed. Consequently, one Gm. of calcium gluconate is often added to one liter of the above solutions, I, II, III, per day.

Solution IV:	Sodium chloride	6.4 Gm.
	Sodium lactate	5.6 Gm.
	Potassium chloride	2.0 Gm.
	Distilled water q.s. ad	1000.0 cc.

Use 1 to 2 liters per day for moderate acidosis, especially in cases of diabetic acidosis in surgical patients.

Solution V:	Sodium chloride	4.25 Gm.
	Potassium chloride	6.0 Gm.
	Distilled water q.s. ad	1000.0 cc.

Use 1 to 2 liters per day for replacement of marked intracellular potassium deficiency. Given by clysis or intravenously.

It is important to realize that with solutions I, II, III, and IV, it is possible to supply the minimal daily requirement of potassium in an adult. However, they will not replace an already existing marked intracellular deficiency of potassium. Darrow has estimated that 3.5 meq./Kg. per day of potassium can be safely administered in a period exceeding 4 to 8 hours.[15] Bellet has administered 1 to 8 Gm. of potassium chloride intravenously in a 1.14% solution to potassium deficient patients over a period of ½ to 2½ hours without harmful effects.[34] Tarail and Elkinton gave their postoperative adult patients between 0.7 and 3.7 meq./Kg. of potassium daily and demonstrated that the cells could retain much of this potassium in excess of nitrogen in a 24-hour period.[12] The most potassium we have ever given a patient parenterally was 10.0 Gm. of potassium chloride, administered in the form of solution V. This was administered by clysis over a period of eight hours without harmful effects being noted. It is safer to give large doses of potassium by the clysis route, as Darrow recommends, than by the intravenous route. For very large doses, we prefer the oral route whenever feasible, as in J. C. and J. G. (Table I). We use a solution containing equal parts of water and syrup of citric acid to disguise the bitter taste of the potassium chloride. This solution may be given to patients in various fluids, such as orange juice or milk. The only undesirable effect we have observed, aside from the unpleasant taste, occurred in one patient in whom diarrhea developed following the administration of 4.0 Gm. of potassium chloride orally.

The main precaution to be observed when giving parenteral potassium chloride solutions is the maintenance of an adequate urinary output. An elevated blood urea N, *per se*, is not a contra-indication to the administration of potassium containing solutions, as may be seen in Table I, in which there are

several patients who had an elevated blood urea N level at the same time hypopotassemia was present. However, we insist on a daily urinary output of over 750 cc. when administering potassium solutions. Adrenal cortical insufficiency, hypocalcemia,[35, 36] shock, severe dehydration with hemo-concentration, severe burns in acute phase, and advanced renal insufficiency[37] are contra-indications, until first adequately treated, or unless a specific indication for potassium can be demonstrated at the start of therapy. The effect of hyperpotassemia on the heart is well appreciated and is to be guarded against by the intelligent use of potassium solutions in a given patient.[38, 39] Daily electrocardiograms and serum potassium levels should be taken if large doses of potassium are being administered.

SUMMARY

1. The prevalence and degree of hypopotassemia in eleven preoperative and postoperative surgical patients maintained on potassium deficient parenteral fluids is presented.

2. The role of alkalosis in accentuating potassium loss from the body is illustrated.

3. The need for parenteral potassium administration in patients subjected to prolonged Wangensteen drainage of the upper gastro-intestinal tract is emphasized.

4. The effect of administering large amounts of potassium to a patient with mesenteric thrombosis in the postoperative period is described.

5. The mechanisms of potassium depletion and the clinical aspects of potassium deficiency in surgical patients are discussed.

6. The quantitative aspects of replacement solutions containing potassium chloride and the precautions and contra-indications governing the use of these solutions are mentioned.

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THE SURGICAL TREATMENT OF PEPTIC ULCER

REPORT OF A YEAR'S EXPERIENCE*

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DURING THE YEAR 1948, 136 surgical pavilion patients with peptic ulcer were operated on at The New York Hospital—Cornell Medical Center. One hundred and forty-seven surgical procedures were done at 139 operations on these patients, distributed as follows:

	Operations	Procedures
Plication for perforation	10	10
Gastric resection	100	100
Gastro-enterostomy	9	9
Vagotomy	20	20
Vagotomy with gastro-enterostomy	..	8
	139	147

The cases reviewed are from the pavilion teaching service. No private patients are included. A large proportion of these patients were operated upon by the resident surgeons under the supervision of the senior staff.

Over the past 16 years there has been a progressive increase in the number of patients admitted to our surgical pavilions with severe symptoms of peptic ulcer unrelieved by medical treatment. It is our impression that this is also true at other clinics similar to ours. This review of one year's experience describes the general nature and gravity of the problems encountered and the principles underlying the policies employed in meeting them.

In general it may be said that surgical treatment in peptic ulcer is reserved for those patients who are not adequately relieved of their symptoms by medical means. This statement, however, needs further explanation. For every five or six patients admitted to our Out-Patient Department whose symptoms of ulcer can be satisfactorily relieved by medical management, there will be one who does not respond to medical treatment or who develops a complication that requires operation.

The common, unequivocal indications for surgery for peptic ulcer are: perforation, obstruction, bleeding and pain.

Perforation. By perforation we mean the penetration of an ulcer into the free peritoneal cavity, producing the signs and symptoms of an acute abdomen. This is treated as a surgical emergency, and no other policy has ever been considered.

Obstruction. Obstruction that is due to cicatrization requires either a short circuiting operation or resection. This again is a situation that can only be relieved by surgery.

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Bleeding. Massive bleeding requires control of hemorrhage. If this can be accomplished by non-surgical means, operation should certainly be postponed. But if it persists, then operation is imperative in order to remove the cause of the bleeding. Repeated massive hemorrhage or minimal bleeding that is persistent, is, in our opinion, an indication for surgical intervention. There is considerable controversy on this point, but within the past decade the surgical treatment of bleeding peptic ulcer has been greatly improved and, with the low mortality rate now associated with gastric resection, the risk to life from operation is definitely outweighed by the probable mortality from bleeding.

Pain. Of the several indications for surgical intervention, pain is often the most difficult to evaluate, since different individuals vary in the amount of pain that can be tolerated. If the pain is incompatible with a person's ordinary activity, and he is thereby prevented from earning his livelihood or participating in his customary pursuits, then operation is indicated. But if the pain is only temporary in nature, and comfortably controlled by simple medication and diet, or even entirely eliminated by a medical regimen, then an operation is not required. Surgery in our clinic is not considered a substitute for medical treatment; it should follow and supplement medical aid. To subject a patient to operation on the premise that a surgical procedure will relieve him of the necessity for care in his diet or for the limitations to activity commonly recommended in the medical treatment for ulcer, would likely result in a continuation of his symptoms, sometimes caused by marginal ulcer.

Perforation and obstruction are, therefore, clear-cut indications for surgical intervention. Bleeding—massive, repeated or continuous—is now being treated more effectively by surgery. Pain, on the other hand, remains a variable that requires careful evaluation and, most important of all, a long trial under medical treatment.

In general, it may be said that the younger the patient the more cautious one should be in undertaking surgery, except in cases of perforation or obstruction. We have seen many patients under 30 years of age with severe symptoms, for whom operation was contemplated but withheld for one reason or another, become well after two or three years; some, indeed, have remained symptom free for 15 years or more. This course of events, however, is less frequent with patients over the age of 40 or 50. Surgical treatment for peptic ulcer, we believe, should be postponed until all medical means have been exhausted unless the common indications for surgery suddenly appear and persist. These are our policies for ulcer patients.

In the group in which the treatment consisted of plication for perforation, there were ten patients, two females and eight males. Their ages ranged from 44 to 61, with a mean age of 52.4 years. Without exception, each of these ten patients gave a previous history of ulcer symptoms. The shortest history obtained was eight months, the longest 30 years. With five, a previous roentgen ray examination had shown a duodenal ulcer. All were admitted within 12 hours after perforation, and were subjected to operation immediately on admission to the Hospital. In each instance treatment consisted of plication of

the lesion. All were duodenal ulcers and only one patient had a postoperative complication, that of a pneumonitis (N.Y.H. 245913).

Two of these ten patients were later subjected to gastric resection, one three months and the other four months after plication. Both of these patients had had a history of ulcer symptoms of more than three years prior to operation.

One of the patients, a male aged 45 (N.Y.H. 499140) had symptoms for 18 years prior to operation in this hospital. He had a perforating ulcer plicated at another hospital 18 months before. Following his N.Y.H. admission, another perforation was plicated, presumably in the same area of the duodenum as the previous one. Four months later this patient was subjected to another operation for the purpose of doing a gastric resection. At the time, there was still marked activity of the ulcer with a great deal of induration in the vicinity of the first and second portions of the duodenum. It was the opinion of the surgeon that gastric resection would have been hazardous because of difficulty in closing the duodenal stump. For that reason a gastro-enterostomy was done.

Of the remaining seven patients, it is likely that all will have continuation or a reappearance of symptoms, even under the strictest medical regimen. Our experience justifies the recommendation of a gastric resection for those patients who have had an acute perforation. This procedure may well be undertaken about three to four months after the perforation, provided the patient has been on optimal medical therapy and there has been roentgen ray evidence of a subsidence of the process.

The indications for operation following an acute perforation are usually obstruction or pain, and sometimes either or both of these combined with bleeding. If a patient is cooperative and can be closely observed, it is probably advisable to postpone gastric resection for six months. However, we have observed such patients to reperforate and thus further delay remedial treatment.

There is an opinion repeatedly expressed in papers dealing with the ulcer problem that acute perforation is frequently the first manifestation of an ulcer. This has not been the experience of our clinic. We have been able to demonstrate a long history of ulcer symptoms in all patients, and often the duration of symptoms recorded on the chart reflects the care with which the history was taken.

Recently, several case series have been reported in which perforation has been treated by intragastric tube drainage, sedation and chemotherapy. We consider this method hazardous and unjustified in view of the low morbidity and mortality rate for patients plicated within 12 hours of perforation.

There were 100 patients in the group subjected to resection for peptic ulcer and in this group the location of the ulcer was as follows:

Gastric	21
Gastric and duodenal	3
Marginal	2
Jejunal colic fistula	1
Duodenal	73
	100

There were 75 male and 25 female patients. The age range was from 34 to 65, with a mean age of 50. The nature of the complaints followed a common pattern. Usually the first symptom was pain followed later by nausea and vomiting, and still later by an intensification of all these and other manifestations of ulcer. The duration of symptoms averaged 10 years, ranging as follows:

Less than one year	10
1- 5 years	29
5-10 years	27
10-15 years	16
15-20 years	11
Over 20 years	7
	100

Thirteen of the patients had previous acute perforations for which plication had been done, and one patient had perforated twice. Obstruction was of clinical significance in 23 of this group, 14 showing partial obstruction that could be relieved temporarily by a medical regimen, and nine complete obstruction that persisted in spite of all ordinary measures employed. Many of the patients had lost weight that was only in part replaced by their medical treatment. Approximately half the total patients exhibited no weight loss and there were also many who were over weight because of having followed an ulcer diet of a high caloric nature.

The significant laboratory findings were (1) degree of acidity and (2) persistence of blood in stools. As to the first, in general the patients showed a hyperacidity on a test meal ranging as high as 140. There were only a few patients with a normal or low acidity and none with anacidity.

So far as blood in stool was concerned, 65 of the patients had more than one negative stool for occult blood during their preoperative period of hospitalization. Six patients, including two who had massive hemorrhage, had no stool examination recorded. The remaining 29 showed persistent positive stools. Bleeding is evidently variable because many patients had a history either of minimal bleeding according to symptoms or evidence of massive hemorrhage prior to their hospital admission, yet during the time of their preoperative preparation they showed no evidence of bleeding within the gastrointestinal tract. It is significant that 48 of the 100 patients had a history of bleeding and of these, 26 had had repeated episodes of hemorrhage. The remaining 52 of the 100 gave no history of symptoms or signs of bleeding.

The earlier operations undergone by some of these patients suggest that their ulcer symptoms were of long duration; this not infrequently caused some confusion as to diagnosis. Four had been subjected to a previous gastroenterostomy, two to vagotomy and 13 to plication for perforation—three of the latter had perforated twice before. Eight patients had had their gall bladders removed and 16 had had an appendectomy.

Preparation for operation after admission to the hospital was rather prolonged, perhaps longer than necessary, ranging as it did from a few hours in instances when operation was undertaken as an emergency for exsanguinating bleeding ulcer, to 40 days. This wide range is the result of the conservative

policy long adhered to at The New York Hospital based on the premise that surgical treatment for peptic ulcer is to be employed only after all possible help from medical means has been exhausted. In general, the preoperative therapy accorded these patients was that of frequent feedings, using additional alkali in an attempt to control pain and rest in bed supplemented by sedation. Patients who had partial to complete obstruction were subjected to either continuous or intermittent decompression. In some instances we have used drip feeding if indicated. Preoperative management of the patient with massive hemorrhage is discussed elsewhere.

The immediate preoperative preparation has consisted of introducing an indwelling gastric tube and evacuating the gastric contents. The preoperative medication of morphine and atropine is determined according to the type of anesthesia to be employed. Each patient is evaluated so that he will be given the anesthesia best suited to his particular needs. Following is a list of the types of anesthesia employed:

Cyclopropane with pentathol	38
Cyclopropane with nitrous oxide	4
Ether and pentathol	43
Ether and nitrous oxide	12
Pentathol plus nitrous oxide plus curare	1
Ether	1
Pentathol and cyclopropane then ether (heart irreg.)	1
	100

The use of the indwelling gastric tube which is continued after operation and aspiration of the bronchial tree at the close of the procedure, accounts in part for the very low incidence of postanesthetic complications that we have experienced. Of several types of operation employed, the posterior polya was the most popular. It was used on 47 patients, and an anterior polya on 26. Actually, it probably makes little difference whether a posterior or anterior anastomosis is made. In 20 patients the Hoffmeister type of anastomosis was constructed; 17 anteriorly and 3 posteriorly. Bilroth II was employed in two patients; the Balfour in one, and a high resection with an esophageal enterostomy in another. For the three marginal ulcers, a dismantling procedure was carried out with additional resection of the stomach.

It is very difficult to judge just how much of the stomach should be removed in these patients. Our policy is to resect at least half but not more than two-thirds in a primary subtotal gastric resection. A review of postoperative films and specimens removed at operation indicates that usually a smaller portion of the stomach is resected than the operator realizes. For this reason we recommend that a full two-thirds of the stomach be removed.

Only two of our four patients subjected to emergency operations for bleeding were good operative risks. The ulcer patient who has an exsanguinating hemorrhage will almost invariably be a poor surgical risk, but this should not deter the surgeon from following the policy of resection. It has been demonstrated by J. D. Stewart,[1] Hoerr, Dunphy and Gray,[2] Warren and Lanman,[3] and by Amendola[4] as well as others, that the earlier the operation is undertaken

—if accompanied by massive transfusion and proper anesthesia—the greater the chance that the patient will go through the surgical procedure without serious complications. A number of patients bleed at first but then stop and can be operated upon later when the risk is extremely low; this fact necessitates a clear policy for patients admitted with hemorrhage associated with peptic ulcer. On our surgical pavilions blood replacement for these patients is begun at once. If transfusion at the rate of 1000 cc. per 24 hours fails to maintain the patient's blood volume and an ulcer is known to exist, then operation is undertaken at once. If, however, a diagnosis has not been established, then roentgen ray examination is made with the operating room in readiness, so that if an ulcer is demonstrated gastric resection may be embarked upon immediately. If an ulcer cannot be found by roentgenogram, then operation is postponed, particularly if there is evidence to suggest that the source of bleeding might be esophageal varices or a malignant tumor.

In general, the older the patient, the more urgent is operation. Signs of peritoneal irritation occurring during hemorrhage usually suggests a perforation which makes operation imperative. The four summaries which follow describe patients who were operated upon for massive, persistent hemorrhage from a duodenal ulcer.

Case 1.—(N.Y.H. 590733.) A 67-year-old woman, known to have been a moderately severe diabetic for 10 years, was admitted to the hospital because of severe abdominal pain of over 3 months' duration. Additional history was unsatisfactory. Two days before admission the patient vomited bright red blood in large amounts. She had two black, tarry stools. Bleeding had evidently continued on the following day, and shortly after admission she vomited approximately 500 cc. of dark red blood and fainted. At the time of admission her Hgb. was 7 Gm., her RBC 2.6. She received whole blood at the rate of 1000 cc. every 12 hours for the following 2 days, but in spite of this the patient continued repeatedly to vomit dark coffee ground material and to pass tarlike stools. Likewise her blood pressure continued to fluctuate and there was no perceptible increase in her hemoglobin or red count. Because of inability to control the hemorrhage she was operated upon and a large posterior wall duodenal ulcer perforating into the pancreas was found, within which there was a free bleeding point from the pancreatico-duodenal artery. A subtotal gastric resection with ligation of the pancreatico-duodenal artery was done. Her postoperative course was uneventful until the eleventh postoperative day, when she developed a left foot drop. It was concluded that she had had an accident to the vertebral artery. From this she gradually recovered and was later discharged from the hospital free of symptoms referable to her gastro-intestinal tract.

Case 2.—(N.Y.H. 247104.) A male, 47 years of age, was known to have a duodenal ulcer for 9 years. This had been only fairly controlled under dietary regimen, and he had seldom been free from symptoms. Two years before, in 1947, patient had vomited coffee ground material and passed tarry stools for 3 weeks. Three days prior to his N.Y.H. admission after a prolonged dietary indiscretion the patient began to have severe abdominal pain, weakness, and he passed numerous tarry stools. On admission to the hospital he appeared ill, was pale, and dehydrated. His hemoglobin was 10 Gm., RBC 3.29 Patient was placed in bed at rest and given fluids intravenously without transfusion. Within 36 hours his hemoglobin was 9 Gm. and his RBC 2.3. He then received 1000 cc. of blood, with an elevation of his hemoglobin to 11.3 Gm. and red count to 3.850. Patient was then put on the usual preoperative ulcer regimen and was making satisfactory progress until his sixth hospital day when, following passage of a tarry stool, he vomited a small amount of bright red blood and fainted. One hour later he vomited approximately

1000 cc. of blood. His Hgb. was then 8.5 Gm. and his red count 2.5. His blood pressure, which previously had been 110/70, began to fluctuate. He was immediately taken to the operating room and with an adequate supply of blood at hand, operation was undertaken. A large callous posterior duodenal ulcer in the first portion of the duodenum perforating into the pancreas was found. Coursing across the base of this ulcer was a large vessel approximately 3 to 4 mm. in diameter which was bleeding freely. A subtotal gastric resection was done and although the pancreatico-duodenal artery was ligated there continued to be considerable bleeding from the ulcer bed in the pancreas. Interrupted sutures were introduced into the substance of the pancreas in an effort to control the hemorrhage. Unfortunately, one of these sutures was evidently placed about the lower end of the common bile duct, for 3 days later the patient became jaundiced and a bile abscess formed which required drainage 2 days later. The course of the patient thereafter was that of peritonitis and uremia, terminating in death 9 days after the first operation and 4 days after the second.

Case 3.—(N.Y.H. 197813.) A male 30 years of age was admitted to the hospital because he fainted shortly after arising in the morning and thereafter had 3 tarry stools. He was believed to have had a duodenal ulcer for more than 3 years. For several weeks prior to his admission he had had increasing abdominal discomfort, most marked in the upper abdomen, which was partially relieved by milk or food. There had been no vomiting. At the time of admission his Hgb. was 12 Gm. and his RBC 3.8. The patient was placed in bed at rest with nothing given by mouth and with heavy sedation, including morphine and phenobarbital. He received fluids intravenously. Late in the afternoon of the day of admission he vomited coffee ground material. The following morning he again vomited and passed a large tarry stool. His blood pressure, which had been stabilized at 120/80 fell to 88/55 and his Hgb. to 8 Gm., his red count to 2.9. In spite of continuous blood transfusions to a total of 1500 cc. there was evidence of continued bleeding without signs of stabilization of his blood pressure. Operation was then embarked upon. A posterior wall ulcer was found in the first portion of the duodenum. No single bleeding point could be demonstrated. A subtotal gastric resection was done. The patient's postoperative course was uneventful and he was discharged from the hospital 12 days after operation. Six months later he remained symptom-free.

Case 4.—(N.Y.H. 499122.) This 50-year-old Irishman was admitted to the hospital because of black stools and weakness of 2 days' duration. For about 8 years the patient had had recurrent episodes of epigastric pain which were relieved in part by food and alkalias. Six years before admission the patient had a period of tarry stools associated with weakness and had been told by a physician that he had an ulcer of the stomach. He was kept on a rigid ulcer regimen but continued to have occasional episodes of pain. The patient had been able to carry on his ordinary activity until two months before admission when he had a severe exacerbation of his epigastric pain which radiated to the back. The pain was only partially relieved by alkalis and although it improved somewhat, it persisted. Two days before admission he first had a tarry stool, which was repeated again the same day, accompanied by weakness. On the day of admission he fainted. On admission to the hospital the patient showed evidence of rather prolonged bleeding, with dehydration. He was placed on nothing by mouth, parenteral fluids and morphine, together with transfusions. His blood pressure became stabilized and over the ensuing 10 days his red count and hemoglobin gradually increased. Ten days after admission to the hospital the patient again began to bleed and roentgen ray examination showed a defective cap, with an ulcer crater posteriorly near the central portion. The patient was then operated upon and an ulcer was found on the posterior wall of the duodenum 1½ cm. distal to the pyloric ring. A subtotal gastric resection, removing approximately two-thirds of the stomach, was done. Patient's postoperative course was uneventful and he was discharged from the hospital with hemoglobin and red count approximately normal. Six months after operation the patient reports that he has remained symptom-free and has returned to his occupation as a minister.

Seventy-six of the 100 patients subjected to gastric resection had an uneventful postoperative course without complication of any kind. The other 24 had a total of 25 complications, which may be divided into two groups—those complications related to the site of the operation and directly connected with the process of healing or re-establishment of the normal function of the stomach and intestine; and those complications unrelated to the local site of operation, or systemic complications. The latter consist of coronary occlusion, mild heart failure, pulmonary complications, thrombophlebitis and acute retention of urine. There was one death.

TABLE I.—*Complications Arising From 100 Subtotal Gastric Resections for Peptic Ulcer, New York Hospital, 1948.*

No complications		76
Gastro-intestinal complications:		
Postoperative gastric retention		14
1- 5 days	6	
6-10 days	2	
11-14 days	3	
Over 14 days (Longest: 30 days)	3	
(No reoperations for retention done.)		
Eviscerations		1
Deaths (peritonitis)		1
Cardiac complication (Mild heart failure)		1
Pulmonary complications:		6
Asthma	1	
Pneumonia	3	
Infarcts		
With signs of thrombophlebitis	1	
Without signs of thrombophlebitis	1	
Vascular complication (Thrombophlebitis)		1
Genito-urinary complication—(Acute retention)		1
Total number of complications in 24 patients		25
Mortality rate for 100 patients: 1 per cent		

The most frequent postoperative complication is malfunction in propulsion of the gastric contents into the small bowel. This condition manifests itself by obstruction. There were 14 of the 24 with this complication, as listed in the accompanying table. Obstruction usually occurs from the seventh to the tenth postoperative day. First, there is a feeling of fullness, soon followed by nausea and usually vomiting. Evacuation of the gastric contents by tube usually brings immediate relief of symptoms, but if the patient is permitted to take fluid or food by mouth, the symptoms are renewed. Roentgen ray studies show that the obstruction is usually incomplete, although there were four of the 14 who exhibited complete retention. The site of obstruction appears to be within a few centimeters of the gastrojejunal junction of the distal loop, and has appeared as early as the second postoperative day and as late as the tenth. The nature of the evacuated gastric contents is similar in each case, consisting of material taken by mouth and the products of the first portion of the proximal loop, namely bile and pancreatic juice. An indwelling gastric tube or repeated evacuations of the stomach, has relieved the obstruction in from one to 31 days, the average time for the group being 8.6 days. The use of antispasmodics

has been found to be of no avail. A careful review of the preoperative histories reveals that in duration and nature of their symptoms they in no way differ from patients who did not have this complication. Likewise there was nothing unusual about their total proteins or their blood picture; nor has the nature of the operation in the past year's experience given us any explanation, since the type of procedure as well as the operators varied throughout the group. The size of the gastric stoma apparently has nothing to do with the complication nor has the nature of the anastomosis which in general has been the same for all gastric resections. This postoperative complication is a disturbing one and has definitely prolonged hospitalization when it occurs.

TABLE II.—*Fourteen Patients with Postoperative Obstruction Following Gastric Resection.*

History Number	Sex	Age	Type of Ulcer	Duration of Symptoms	Preop. Prep. (Days)	Type of Operation*	Duration of Complication P. O. From	Days To	No. Days	Degree of Obstruction
1. 236645	F	77	Gastric	One year	4	Polya post.	10th	11th	1	Partial
2. 236504	F	35	Duodenal	13 years	7	Polya post.	9th	19th	10	Partial
3. 62054	M	53	Duodenal	4 years	10	Polya post.	7th	19th	12	Partial
4. 319534	M	47	Duodenal	8 years	8	Polya post.	3rd	17th	14	Complete
5. 380598	M	44	Duodenal	15 years	11	Polya post.	3rd	34th	31	Complete
6. 400237	M	56	Duodenal	4 years	6	Polya ant.	9th	16th	7	Complete
7. 433270	M	50	Prepyloric	1 year	7	Polya post.	3rd	19th	16	Complete
8. 497859	M	34	Duodenal	7 years	14	Polya post.	10th	12th	2	Partial
9. 503627	M	49	Duodenal	6 years	10	Polya post.	9th	11th	2	Partial
10. 505852	F	54	Duodenal	2 years	4	Polya post.	9th	10th	1	Partial
11. 505895	M	52	Gastric	2 mos.	5	Polya ant.	6th	7th	1	Partial
12. 75823	F	49	Duodenal	2½ mos.	2	Polya post.	9th	10th	1	Partial
13. 486463	F	45	Duodenal	6 years	12	Polya post.	8th	20th	12	Partial
14. 486423	F	45	Duodenal	6 years	10	Polya post.	8th	18th	10	Partial

* All the operations were polya posterior, except No. 6 and No. 11 which were polya anterior. All except No. 2, with ½, and No. 10 with ¾, had ⅔ of the stomach removed.

The attached table of 14 patients shows that we have used no specific therapy to relieve this complication, save that of decompression with an intragastric tube. That edema of the wall of the structure involved might be a factor and might possibly be associated with either serum proteins, anemia or overhydration, led us to further evaluate the blood picture. We have obtained no revealing information from this study, however.

Nine patients, seven males and two females, with ages ranging from 45 to 70, were treated by gastro-enterostomy. The average age was 59.3 years. In each instance there was specific justification for doing a gastro-enterostomy rather than a gastric resection. Age and general debility, associated with some specific organic disorder in addition to the ulcer, were the indications for the minimal procedure in five of the patients. With the other four, a gastro-enterostomy was done because it was felt a gastric resection would have made closure of the duodenal stump hazardous. When there is extensive involvement of the posterior wall of the distal portion of the first part of the duodenum, there is likely to be great difficulty in securing a satisfactory duodenal closure after removal of the ulcer. Because a good portion of the reported mortality

following gastric resection has been from peritonitis secondary to leakage from the duodenal stump, it has been our policy to avoid transecting the duodenum under these circumstances. That this policy has not been abused is attested by the fact that during 1948, 100 gastric resections were performed and only four gastro-enterostomies performed for what were considered unsatisfactory conditions for resection of the stomach. The remaining five of the nine gastro-enterostomies were done because of other than local findings. During the year we did not employ the method of pyloric exclusion as introduced by Finsterer[11] or modified by Allen and Welch.[12]

Of the 136 patients, 20 were subjected to vagotomy as described by Dragstedt[5] and of these three were transthoracic, eight were subdiaphragmatic and nine were subdiaphragmatic combined with gastro-enterostomy. There were 18 males and two females in this group and the ages ranged from 28 to 55, with a mean of 46 years. Four of the patients had marginal ulcers of which two were secondary to posterior gastro-enterostomy and two to gastric resection. The remaining 16 ulcers were duodenal.

The transthoracic vagotomies were performed for duodenal ulcer in one case and for marginal in two.

Eight patients were subjected to subdiaphragmatic vagotomy as a primary procedure for duodenal ulcer. All eight had extremely high acids preoperatively; in all but one the physiologic vagotomy was demonstrated postoperatively. A subdiaphragmatic vagotomy was performed on one patient for marginal ulcer which followed gastric resection done four years earlier. He had had symptoms for a year and a half and hemorrhage two and one-half weeks before admission.

A subdiaphragmatic vagotomy with gastro-enterostomy was performed nine times. These nine patients had, besides their duodenal ulcers, sufficient signs of obstruction to warrant the belief that they might be seriously obstructed after vagotomy and the accompanying atonia.

Of the three patients who had transthoracic vagotomies, only one has been free of symptoms and without roentgen ray evidence of an active ulcer. One developed fullness, nausea, diarrhea and belching following operation. This improved under treatment with urocholine and at the end of six months he was better but not well and had been unable to regain the weight lost. The third patient, who had a transthoracic vagotomy for marginal ulcer following a gastric resection done four years before, continues to have some epigastric pain, although the roentgenogram indicates healing of the ulcer.

Two of the eight patients on whom a subdiaphragmatic vagotomy was done as a primary procedure for duodenal ulcer had symptoms after operation; in one case transient fullness after eating subsided after six months; in the other nausea, fullness and inability to eat persisted. He was subjected to gastric resection and since then has been symptom-free.

One patient, who had a vagotomy for marginal ulcer which developed a year and a half after a gastric resection and who bled for two and a half

weeks before admission, required lysis of adhesions for signs of intestinal obstruction. Three months later he was free of symptoms and roentgen ray showed complete healing of the marginal ulcer.

Of the nine patients who had a combination of subdiaphragmatic vagotomy and gastro-enterostomy, three had postoperative complications. The first had a brief period of respite from symptoms and then, recurrence of pain, nausea and vomiting. His was a marginal ulcer and he is advised to have a gastric resection in the near future. The second was troubled by diarrhea for a month after vagotomy but this subsided gradually. The third patient had postoperative bronchial pneumonia from which he recovered without event.

No vagotomies have been performed for gastric ulcers. Subdiaphragmatic vagotomy is most successful in the treatment of marginal ulcers. If vagotomy is performed as a primary procedure in duodenal ulcers the region of the stomach adjacent to the ulcer and the duodenum should be inspected to ascertain the presence or absence of other lesions.

In comparing the immediate results of vagotomy with those of gastric resection and gastro-enterostomy it is evident that resection is by far the most satisfactory as proved by a long follow-up study from this clinic. Our analysis also suggests that vagotomy is not advisable as a primary procedure in duodenal ulcer. Not only does it sometimes fail to relieve ulcer symptoms, but adds to them other disagreeable features. It has also been evident that a physiologic vagotomy demonstrated by the response to an insulin test immediately after operation may show a return of gastric function within six months to a year. It is our opinion that the longer the lapse of time after vagotomy, as is true for other operative procedures for ulcer, the greater will be the incidence of complications and unsatisfactory results.

The large number of articles now appearing in the literature with an ever increasing follow-up on patients with vagotomy are establishing limitations for this procedure. Grimson,[6] Moore,[7] Colp,[8] Walters[9] and Beal[10] have in recent publications voiced a common opinion that the physiologic effects of vagotomy may not be permanent. This holds for those that are favorable in the treatment of ulcer as well as those that are considered undesirable side effects. The problem concerning vagotomy in the treatment of ulcer is: Does it contribute to interruption of this disease and at the same time avoid those complications that are associated with other surgical procedures over a long follow-up period? It is our opinion that resection of two-thirds of the stomach is the most satisfactory procedure to employ and that vagotomy should be reserved for those patients who develop marginal ulcer following resection. It is not a matter of the mortality rate for the two procedures, since we believe the rate for both is extremely low.

Surgical treatment for peptic ulcer should not be carried out by rule of thumb for each patient requires individual evaluation. The objective is to relieve the patient of his symptoms with as little risk as possible. From our overall experience we believe that gastric resection is the surgical procedure that

will offer the greatest degree of relief. At the same time it should be emphasized that there are certain contra-indications to gastric resection, most of which are associated with the increased risk to the patient that this procedure imposes.

A review of the patients treated at The New York Hospital by gastro-enterostomy reveals that gastric resection was not done because, first, the patients' general condition rendered them poor operative risks for the radical procedure and the simpler procedure was preferable; and second, the condition of the tissues in the immediate vicinity of the ulcer—which was most frequently a duodenal ulcer perforating into the pancreas—was such that satisfactory closure of the duodenal stump was considered improbable by the operator. It has been stressed repeatedly by those reporting their experience with subtotal gastric resection that one of the most frequent causes of death postoperatively is peritonitis, the result of leakage from a duodenal stump. Our overall policy keeps this hazard before the surgeon and is, we feel, in part responsible for our having avoided this catastrophe for one year at least. The actual number of patients for whom gastric resection was believed contra-indicated was small—four to a hundred resections. Indeed, the one patient who died in this series might have been better treated by a gastro-enterostomy or by exclusion as advocated by Finsterer,[11] Allen and Welch[12] and others because it was the size of the lesion and the reaction of the adjacent structures that so obscured the anatomical relationships that the surgeon placed a suture about the common bile duct, leading to obstruction and eventually to death.

In 1948, 136 patients with peptic ulcer were operated upon, and 139 operations were performed. The location of the ulcer and the operations is as follows:

	Plication	G.R.	G.E.	Vagotomy alone	Vagotomy and G.E.	Total
Gastric	0	21	0	0	0	21
Gastric and duodenal	0	3	0	0	0	3
Duodenal	10	73	9	8	8	108
Marginal	..	2	..	4	..	6
Jejuno colic	..	1	..	..	..	1
	10	100	9	12	8	139

All gastric ulcers were treated by gastric resection. During this period we encountered one carcinoma of the stomach that had been diagnosed benign ulcer preoperatively. Only three instances of double ulcer, gastroduodenal, were encountered. These were treated by gastric resection. Six marginal ulcers, two secondary to posterior gastro-enterostomy and four following gastric resection were found. Two of these were treated by further resection of the stomach and four by vagotomy. One hundred and eight of the 139 ulcers were duodenal, of which ten were associated with free perforations that were plicated. Seventy-three were subjected to subtotal gastric resection, nine to gastro-enterostomy because of one contraindication or another and 16 to vagotomy,

eight of which had, in addition, a gastro-enterostomy. One gastro-jejuno-colic fistula was treated by further resection of the stomach and of the jejunum and colon at the site of the lesion. There was one death following gastric resection for massive and persistent hemorrhage of a posterior wall duodenal ulcer. The postoperative complications that occurred were of two general types, those of a systemic nature commonly associated with major surgical procedures and those related directly to the function of the gastro-intestinal tract. These have been described in detail.

In a recent report from the Presbyterian Hospital (New York), St. John, Harvey, Ferrer and Sengstaken[13] reported 394 partial gastric resections performed over a period of ten years, from 1936 to 1945, with follow-up results that led them to conclude that this is the surgical procedure of choice. They have also noted that their mortality rate for resection fell from 20 per cent in the decade from 1916 to 1925 to 4.6 per cent for the decade of 1936 to 1945.

Heuer[14] reported in 1939 a total of 142 partial gastric resections for peptic ulcer from this clinic with a mortality rate of 7 per cent and 5.7 per cent for the last 105 cases. Since 1939 we have observed a very gradual but definite decrease in this rate. In 1948, 100 consecutive resections for peptic ulcer were done with only one death, a mortality rate of one per cent.

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DUODENAL FISTULA — PROBLEMS IN MANAGEMENT*

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THE SUCCESSFUL TREATMENT of intestinal fistula has long been a serious problem. Despite accumulated experience, certain types of fistulas remain difficult to correct. This is particularly true of duodenal fistulas, among which Bartlett and Lowell[2] in 1938 found a 37 per cent mortality in 128 patients. Colp[5] reported a 51 per cent mortality in 61 cases.

Emphasis is placed here on the management of the acute, postoperative, external, duodenal fistula with a view toward outlining a program that has in our experience led to successful closure.

Duodenal fistula, as contrasted with external intestinal fistulas in general, combines the problems peculiar to high level fistulas with certain additional problems related to its specific duodenal origin. Normally, the gastro-intestinal tract accepts proximally huge quantities of fluid and electrolytes, a large proportion of which are re-absorbed further along the tract. Duodenal fistula, being a high-level gastro-intestinal outlet, rapidly depletes the organism, with far-reaching effects. Massive fluid and electrolyte loss, deranged gastro-intestinal motility, and certain profound chemical changes in the blood, are seen. Up to seven liters a day, containing as much as 2.5 Gm. of sodium chloride may be lost through the fistula even though nothing be taken by mouth. The chief fluid losses through a fistula of the duodenum are swallowed saliva, gastric, duodenal, pancreatic, and biliary secretions. Evidence of disturbed gastro-intestinal motility may be found in the frequently observed partial collapse of the intestine distal to the fistula, and in occasional dilation of the short proximal segment. Blood chemical changes are characteristic, with depressed chloride, elevated CO_2 combining power and non-protein nitrogen levels. Thus, as in high intestinal obstruction, the untreated patient with a duodenal fistula is confronted with starvation, alkalosis, dehydration, and uremia.

Since the most active and copious digestive ferments are found in the upper portion of the gastro-intestinal tract, it is readily understandable that problems arising out of their spillage will be specifically encountered with duodenal fistula. Such a fistula conveys to the skin pancreatic trypsinogen which has been activated by enterokinase by the duodenal mucosa. This activation creates active trypsin. The enzyme, trypsin, gains its optimal pH in the alkaline medium found in duodenal bile. Management of a duodenal fistula is, therefore, complicated by enzymatic tissue-protein digestion, with the result that trypsin attacks the abdominal wall and skin. As intestinal contents successively distal to the duodenum are drained to the skin via fistulas at successively lower levels, correspondingly less skin digestion is encountered.

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The four chief causes of persistence of a fistula in any part of the body have long been recognized as: (1) the presence of a foreign body; (2) communication with a hollow viscus; (3) the existence of a granulomatous disease (tuberculosis, actinomycosis, lues); and (4) carcinoma in the tract. Duodenal fistula is no exception. It persists in addition, however, by the specific digestive action of the very secretions passing through it (Ochsner[20]).

The duodenal fistula may result at operation in many ways. Excessive stripping of blood supply in duodenal stump closure during gastrectomy, strangulating sutures during such closure, inexact hemostasis with resultant uncontrolled or delayed hemorrhage, or drains so placed as to cause pressure necrosis, may lead to fistula formation. Drains placed next to a suture line so as to draw agglutinating fibrin away from the fresh anastomosis, may result in a fistula. Accidental injury to the duodenum consequent upon removal of a diseased, adherent, right kidney, or biliary tract surgery with rupture of the

TABLE I.—*Causes of Duodenal Fistula in 61 Cases**

Gallbladder Surgery	23
Duodenal Ulcer Perforation	14
Nephrectomy	10
Resection of Stomach	6
Traumatic Rupture of Duodenum	6
Carcinoma of Pancreas	1
Intestinal Tuberculosis	1
	61

*Colp: Ann. Surg., 78: 725, 1923.

common duct at the sphincter of Oddi level, and operations in and about the duodenum, such as suture necrosis or leakage of omental graft following closure of a perforated duodenal ulcer, have at times resulted in fistula (Table I). Trauma has resulted in fistula formation. Not only penetrating stab and gunshot wounds or foreign bodies within the intestinal lumen (e.g., toothpick, fish bone), but also non-penetrating abdominal blows, may be a starting point. The latter are most apt to occur as crushing injuries after a recently ingested meal, and involve especially retroperitoneal areas near bony prominences where the intestine is immobile. If fatal peritonitis does not follow, abscesses may lead to fistula formation, especially when these abscesses are drained.

The fistula with distal obstruction creates an additional problem, namely removal of the obstruction, or short-circuiting around it (e.g. by gastroenterostomy). Those associated with a foreign body obviously require its removal. Carcinoma and granulomatous disease in association with duodenal fistula present special problems related to the treatment of the underlying pathologic condition. Traumatic and operative fistulas, however, with or without abscess formation, represent the bulk of duodenal fistulas. Among these, the differentiation between "lateral" and "end" types (Fig. 1) was wisely emphasized by Bartlett and Lowell[2] in 1938. In the "lateral" type, continuity of the intestinal tract is preserved, and there was found a 40 per cent mor-

tality among 114 cases. The "end" type duodenal fistula is most often represented by absence of intestinal continuity, as exemplified by the blind duodenal stump blow-out following gastrectomy. Here the mortality was 14 per cent in 14 patients cited by Bartlett. The differentiation of these two structural types of duodenal fistula is, therefore, manifestly of prognostic importance.

Ingenious methods have been devised to correct duodenal fistula. As Bartlett and Lowell[2] point out, it is not so much the method used as the care and meticulousness of its application in the individual patient which will make for ultimate success or failure. All methods are directly aimed at three main goals: (1) prevention of tissue digestion by pancreatic enzymes; (2) maintenance of fluid, electrolytes, and nutritional balance; and (3) ultimate closure of the fistula and restoration of continuity of the intestinal tract. The methods are both conservative and operative. Their selection will depend on the type and cause of the fistula, and upon the general condition of the patient when first seen. If the patient shows marked inanition, dehydration, and painful inflammation of the abdominal wall, he is not a proper candidate for a major surgical excision, exclusion operation, or shunting procedure. Conservative methods will be needed, perhaps for a long period, before definitive surgery may be attempted. The conservative measures may themselves solve the problem.

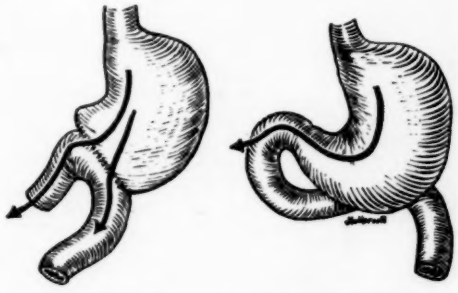

FIG. 1.—Types of Duodenal Fistulas.

Five patients with duodenal fistula, and the methods used in their management, are summarized below. Three patients were personally treated during the past five years. Two additional cases, one in 1923 and one in 1934, were found in the records of the Massachusetts Memorial Hospitals between 1914 and 1944.

Case 1.—K. B., a 27-year-old infantryman, was shot in the epigastrium while manning his machine gun near Aachen, Germany, on October 4, 1944. Despite wounding, he continued in action, killing 7 of the enemy and taking 15 prisoners, for which he received the Silver Star. Laparotomy the following day revealed a lacerated left liver lobe. The bullet was left in the spinal musculature next to L 3 vertebra, which was fractured.

Two months later, while the patient was under our care in an overseas general hospital, strongly alkaline clear fluid, giving a positive amylase test for starch digestion, flowed from the laparotomy wound. This sinus tract was explored, found adherent to the abdominal wall, liver, omentum and stomach, finally entering a fibrous mass adherent to the pancreas and posterior aspects of the stomach. Postoperatively, a fecal fistula developed in the lower end of the wound.

Six months following wounding, the patient was still draining considerable amounts of clear fluid from the upper end of his wound, and purulent material emerged from the lower end. The patient had lost weight from 150 pounds to 79 pounds, and had suffered

considerable inflammation of the abdominal wall. He was treated by N/10 hydrochloric acid wound drip, intravenous fluids, amino acid, and whole blood transfusions with massive vitamin therapy and several incisions and drainages of a recurrent epigastric abscess. This abscess formed whenever the upper wound drainage temporarily was closed off. At these times he suffered pain, fever, and shortness of breath, relieved by probing and spreading of the wound. This drainage was collected by suction, mixed with soup, and re-fed by tube in an endeavor to increase nutrition, combat avitaminosis, and correct trypsin digestion of the skin. Lipiodol with roentgen ray study of the wound sinuses demonstrated a left subphrenic cavity communicating with the transverse colon and pancreatic duct.

FIG. 2.—(Case 1.) Examination four years and two months after wounding reveals excellent nutrition and a well-healed upper quadrant incision with no suggestion of weakness or hernia.

After a 4 pound weight gain, laparotomy was performed 7 months after injury by Lt. Col. Lewis S. Pilcher on May 25, 1945, and a duodeno-transverse colonic-cutaneous fistula was found. This was excised, with resection and closure of the duodenal segment followed by end-to-end anastomosis of the transverse colon. A decompressive cecostomy was provided. The fecal fistula and the duodenal fistula never drained again following this procedure. After removal of the tube, the cecostomy wound healed rapidly. The residual abdominal wall inflammation rapidly cleared and the patient gained one-half pound a day for 13 days, when he went home on furlough. The patient re-entered briefly for incision and drainage of a wound abscess, following which he gained weight again on forced feedings. In January, 1946, a ventral hernia was repaired. The patient was honorably discharged with partial disability in May, 1946, weighing his original 150 pounds.

Subsequent to discharge, this veteran has worked part-time as a taxi-driver, and has been re-admitted 8 times to the Veterans Administration Facility for exhaustive investigation of "indigestion," post-prandial epigastric cramps, and a feeling of fullness, occasional nausea, and constipation. Repeated G.I. series and barium enemas have revealed little to account for his complaints, and he has been managed by dietary regulation and mineral oil.

Examination in December, 1948, 4 years and 2 months after wounding, revealed the excellent nutrition exemplified in the accompanying photograph (Fig. 2), and a well-healed upper quadrant incision with no suggestion of weakness or hernia. Gastrointestinal roentgen ray studies revealed marked pyloric spasm with narrowing of the distal duodenum. There was a temporary delay in the mid-portion of the descending duodenum. Barium passed without obstruction through the remaining duodenum. The duodenal cap was not clearly visualized. Two and one-half hours after barium meal showed the stomach to be only half empty. There was a marked deficiency pattern of the small bowel. The bullet and shell fragments were seen, as on previous examination.

This is the history of the remarkable recovery of a patient who seemed certain to die from progressive wasting and starvation during the seven and one-half months between wounding and radical operation. When his weight fell to 79 pounds, forced massive high vitamin feedings by gavage were tried and led only to nausea and vomiting. Great courage was displayed in the surgical approach to correct this desperate situation, and in view of the difficulties, an excellent result was gained in rehabilitating this patient. He came from Vermont in December, 1948, to see us, four years and two months after his battle injury.

The remaining bullet and shell fragments still cause no symptoms. The duodenal fistula drained for seven and one-half months until operative correction, and it proved a frustrating problem to the patient and to us. Relief from wound irritation and digestion was obtained for long periods by allowing the patient to keep the fistula dry by applying suction himself throughout the day, as suggested by Lanman.[15] This kept the patient occupied and active in his treatment and helped his morale. Superficial wound healing was followed repeatedly by abscess, requiring drainage.

The colonic fistula developed two months after wounding and probably resulted from duodenal and pancreatic secretions plus regional infection within the abdomen. It is noteworthy that following radical operation, the patient had a voracious appetite, gained weight rapidly and left the hospital on his thirteenth postoperative day. The remaining partial obstruction of the duodenum requiring dietary care was not producing sufficient discomfort in December, 1948, to indicate intervention by gastrojejunostomy.

It has recently come to the attention of the authors that on March 16, 1949, this patient underwent subtotal pancreatectomy, fistulectomy, and splenectomy by Dr. Walter B. Crandell, Chief, Surgical Service, Veterans Administration Facility, White River Junction, Vermont. Serum-amylases were 400 and 500 mg. per 100 cc. preoperatively. Pathology report was chronic pancreatitis. He developed a temporary postoperative gastro-cutaneous fistula which had closed on discharge.

Case 2.—L. E., a 58-year-old male with a strong alcoholic background was admitted May 12, 1943, seven hours following perforation of a recurrent duodenal ulcer. The perforation was closed by an immediate operation. Three and one-half years later a similar procedure was carried out seven hours after a second perforation. This closure was accompanied by the use of Penrose drainage "down to the region of the first portion of the duodenum," the drain being brought out through a stab wound in the flank. The patient developed a large abscess mass 29 days following operation, which at the time was considered to represent a residuum of peritoneal contamination. This ruptured and drained through the stab wound in the flank and was followed by intermittent drainage from an apparently superficial wound sinus.

Forty-eight days following closure of the second perforation the patient underwent a three-quarter anterior gastrectomy with removal of the duodenum one inch distal to the pylorus. No fistula was revealed at the time of this procedure. Postoperatively, the patient continued to drain one to 2 tablespoonfuls daily of cloudy exudate from the wound of his previous operation. Redness and maceration of the skin over a diameter

of 6 to 8 cm. around the external opening of the fistula became apparent. This was treated by skin protection by Fuller's Earth (Kaomagma) and zinc oxide applied locally. Methylene blue by mouth appeared promptly in the urine, but not on the abdominal dressing. A ureteral catheter was introduced into the sinus for some considerable distance and lipiodol injected into it. This catheter was seen by roentgenogram to reach the vicinity of the duodenum and the dye to enter that organ.

Drainage became sparse and intermittent but persistent in subsequent months, so that skin reaction and general nutrition did not constitute a problem. The patient has maintained his weight of over 140 pounds. He continues to drink to excess. The fistula was still draining eight and one-half months following closure of his second ulcer perforation, and seven months following gastrectomy. A recent follow-up visit reveals that sinus drainage had finally cleared in March, 1948.

However, the patient has had two episodes of bad abdominal cramps and vomiting for which he was hospitalized in August, 1948, for a week, and again as an emergency in November, 1948, when he underwent cholecystectomy for stones and drainage of a pancreatic abscess. He lost weight from 165 pounds to 115 pounds. The patient has recently been draining a small amount of serous material from a new abdominal opening, which has been probed to a depth of 3 inches, located just medially to the old healed sinus. His present weight is 130 pounds.

This patient illustrates the tenacious persistence of duodenal fistula in a troublesome though less dramatic guise. This fistula resulted from the original perforated ulcer. Unlike the soldier (Case 1), this man did not show early marked inanition, electrolyte imbalance, or skin and abdominal wall digestion. The patient bore the fistula well during its persistence for seven months after gastrectomy. Excessive chronic alcoholism was evident at follow-up examinations, and this was felt to be related to his recent acute pancreatic abscess.

The "pancreatic abscess" followed by the serous drainage from a new opening subsequent to cholectystectomy, in our opinion represents persistence of the fistula.

Case 3.—M. O. S., a 57-year-old housewife, underwent a difficult urologic operation, namely a right nephrectomy for chronic pyonephrosis and nephrolithiasis complicated by perinephric abscess, scarring, and distortion. Following mobilization of the kidney, a transverse tear into the duodenal lumen was recognized at operation, and immediately closed in two layers with continuous 0 catgut sutures. Three Penrose drains were inserted deep into the wound, and three grams of sulfanilamide dusted into the wound.

A stormy convalescence was complicated by jaundice on the second postoperative day, and spontaneous outpouring of what appeared to be pure bile on the fourth postoperative day. Skin maceration rapidly set in and carmine dye given orally appeared promptly on the flank dressing. It was obvious that a duodenal fistula of the lateral type had occurred.

Fluid balance and alimentation became a problem. Up to 1000 cc. daily were lost through the fistula. Blood chemical changes characteristic of duodenal fistula supervened with depleted chlorides, elevated CO_2 combining power and N.P.N. and reduced total protein. Massive fluid and electrolyte therapy, up to six liters a day, were required.

A feeding jejunostomy was made on the sixteenth postoperative day. Wangensteen suction was applied to the fistula in the right flank, and this drainage was collected and re-fed through the jejunostomy. The patient rapidly developed foul, frothy stools. This complication was successfully combated by chilling the drainage before refeeding, so as to preserve its full enzymatic activity. Jejunostomy feedings at the rate of 150 cc. an hour,

with soft solid diet by mouth, were excellently tolerated without cramps, distress, or complaint. Parenamine solution was put into the jejunostomy, 4 liters daily, along with fistula drainage. These feedings contained 2 Gm. of salt daily. Control of the fluid and electrolyte balance is compositely shown in Figures 3 and 4.

Twenty-three days after nephrectomy, and 8 days following jejunostomy, the suction to the duodenal fistula was discontinued. By this time, the blood chemistry level had returned to normal except for the total protein, which remained low.

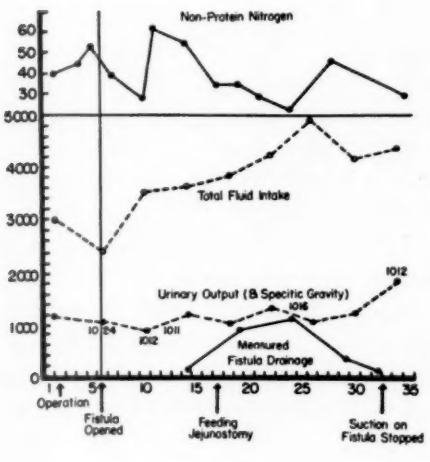

FIG. 3

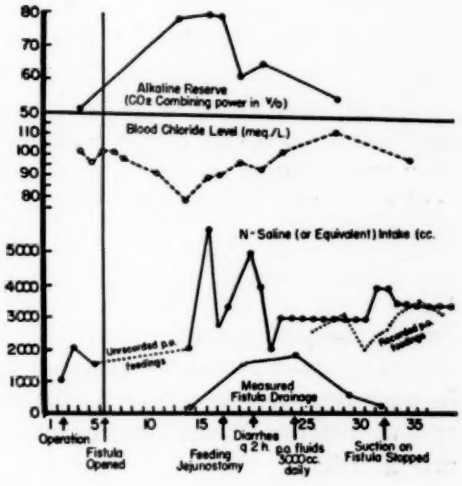

FIG. 4

FIG. 3.—(Fluid Balance in Case 3.) It is apparent from this graph that the loss of duodenal secretions was accompanied by a rise in N.P.N. This nitrogenous accumulation reverted to normal, pari passu, with increased fluid intake to cover the loss.

That fluid balance was well maintained in this patient is suggested by the adequate (1000 cc. daily) and even slightly increased urinary excretion throughout the period of measured fistula drainage.

FIG. 4.—(Electrolyte Balance in Case 3.) Depressed chlorides with concomitant increased CO_2 combining power (alkalosis) occurred with the opening of the fistula. These were reverted to normal by massive normal saline (or equivalent) intake while the fistula remained open.

One month following her original operation, there was marked improvement. The total protein rose to 6.24 and the N.P.N. fell to 28. Wound drainage became much less and the jaundice had entirely disappeared. The jejunostomy tube was removed 25 days following its insertion, and 40 days following her original nephrectomy. Five daily dressings were required for persistent fistula drainage at this time. However, this drainage decreased and was only slight on discharge, 35 days following jejunostomy and 50 days following her original operation.

Recent follow-up reveals that 2 years since discharge the patient is well, gaining weight, and asymptomatic. The fistula persisted for two months after operation, and has been healed for 2 years.

This patient illustrated a duodenal fistula at its worse. Its inception following difficult nephrectomy is not unusual, and it is to be noted that the fistula

developed despite the fact that the duodenal tear was promptly recognized and sutured at the time of the original nephrectomy.

It is in relation to fluid and electrolyte balances that this case is especially instructive. These phases are separately presented in graphic form and illustrate specific therapeutic points (Figs. 3 and 4). With the onset of fistulous drainage, fluid replacement was delayed and the one remaining kidney, conserving fluid, was thereby prevented from clearing nitrogenous waste. The nonprotein nitrogen was cleared from the blood, *pari passu*, with increased fluid intake matching fluid loss. At the peak of the fistulous drainage, such fluid replacement entailed *over five liters of normal saline solution*, or its equivalent, in a single day. That fluid balance was well maintained in this patient is suggested by an adequate (1000 cc. daily) urinary excretion without undue urinary concentration throughout the period of measured fistula drainage.

Fortunately, the one remaining kidney in this patient was capable of performing normal renal function not only in the clearance of nitrogenous waste, but in the restoration of normal acid-base balance as well (Fig. 4). Figure 4 shows a typical blood chloride depression and relatively elevated alkaline reserve consequent upon a primary chloride loss via the fistula. With the exhibition of adequate replacement therapy in the form of normal saline solution or its equivalent, and later by refeedings of fistula drainage into a jejunostomy, and with normal renal function, this acid-base dislocation was reversed to normal values.

Case 4.—Mrs. H. B., a 47-year-old housewife, underwent a difficult cholecystectomy for chronic cholecystitis and cholelithiasis through a right upper quadrant transverse incision in 1934. Penrose drainage was used. Twenty-three days following operation, the wound was explored under gas-oxygen anesthesia because of a suspected deep abscess. This proved to be the size of an orange, resting in the gallbladder bed. There was no evidence of subphrenic abscess at operation. The abscess was drained with Penrose drains, and the wound closed. Six days following the second procedure, a profuse foul-smelling drainage was found on the dressing, and the drains were removed. Redness and skin excoriation rapidly developed. The patient continued to drain profusely and had marked weakness and depression. Her condition was poor. Seventeen days following the second operation, barium by mouth was seen under fluoroscopy to leave the gastrointestinal tract at the most dependent portion of the duodenum. At this time the patient was severely dehydrated and semi-comatose. Kaolin and albumen powder with petroleum jelly gauze was used on the wound edges for skin protection.

No suction to the fistula was employed, but frequent dressings were utilized. Fluid balance was not maintained, and this patient's recorded urinary output from day to day revealed the total daily amount never exceeding 450 cc., and was often considerably below this. Intake utilized rectal taps, supplemented by inadequate, occasional, small intravenous of 5 per cent dextrose in saline in amounts of 500 cc. The blood chemistry was not followed save for a fasting blood sugar of 105 and an N.P.N. of 35, 10 days following the cholecystectomy.

During the course of the patient's illness, at all times she was allowed fluid, including milk, much of which was vomited and some appearing on the abdominal dressing. Twenty-two days following the second operation, and 26 days following cholecystectomy, the patient expired.

Postmortem examination, limited to the incision, revealed the gallbladder to be clean, with a few adhesions to the duodenum. Hepatic and common ducts were patent,

but slightly dilated. An 8 mm. opening in the first part of the duodenum, about one cm. from the pylorus, led into the sinus tract, leading in turn to the transverse operative wound. Through this sinus tract, stomach contents were readily expressible. The ampulla of Vater was located approximately 5 cm. below the described duodenal opening, and appeared normal. No evidence of abscess was found. The final anatomical diagnoses included chronic cholecystitis, toxic myocarditis, hypostatic congestion of lung, toxic hepatitis, fatty metamorphosis of the liver, toxic nephritis, and acute nephritis. Microscopic examination of the sinus tract revealed it to be lined with connecting tissue markedly infiltrated with lymphocytes and plasma cells. It contained a large thrombosed vein.

As compared to the previous patient who survived and was cured, this case, treated 13 years previously, shows obvious failure to appreciate the value of massive fluid and electrolyte replacement. The postmortem findings do not point out the patent physiologic death from dehydration, alkalosis, coma, and uremia which supervened. Without correction of the above deficiencies, the patient survived 22 days following establishment of the fistula. As in the previous case, this patient had the more serious "lateral" type of duodenal fistula.

Case 5.—Mrs. M. H., a 43-year-old housewife, was admitted January 26, 1923, with a draining abscess in the right lumbar region. A preoperative impression following a cystoscopy was that of tubercular pyonephritis on the right. Following direct transfusion by the Kimpton method, a difficult nephrectomy was performed. The patient was in profound shock following clamping and division of the renal pedicle, but was revived by "shock enema of coffee." Twelve days following operation, the wound was explored under general anesthesia down to the duodenum around the sinus tract. An opening was made in the anterior surface of the duodenum near the pylorus, through which the finger was inserted in order to locate the fistula, which was found 3 to 4 inches away from the pylorus, close to the median line. This was separated from the posterior abdominal wall, and was sutured with two rows of No. 2 green catgut and one row of fine Pagenstecher. The opening which had been made higher up in the duodenum was closed in the same way. Two Penrose drains were inserted into the peritoneal cavity and the wound was closed in layers. Convalescence was uneventful following the second operative procedure, and the patient was discharged on her twenty-first postoperative day.

Wound cultures reported gram positive bacilli and diplococci, streptococcci, and gram negative bacilli. Analysis of wound drainage prior to fistula closure was reported "gastric contents," bile absent. A pathologic examination of the removed kidney revealed nephrolithiasis and no evidence of tuberculosis. No mention is made in the record of the patient's fluid gains, fluid balance, or of her fistulous fluid losses. Apparently, skin digestion and maceration did not create a problem, as this is not alluded to in the record.

It must be pointed out in relation to this case that operation with primary closure in the presence of duodenal fistula is not usually associated with the success and seeming simplicity which this brief record implies. The wound is invariably infected, the tissues are partially digested, sutures cut through, and healing usually fails.[5, 6, 12, 14, 17-19] It has been the experience of numerous operators that such attempts have been largely doomed to failure, with prompt recurrence of the fistula, leaving the patient in worse condition than before. Further, these depleted patients are usually unfit to stand the operation because

of starvation, alkalosis, dehydration, and uremia. Despite the successful outcome in this instance, such a method of treatment should be mentioned principally in order to be condemned. Its use in a chronic, minimal, mucus fistula should, as will be seen, probably be confined to the retroperitoneal approach.[5]

Confronted by a patient with a duodenal fistula, the diagnosis must include thorough studies to discover complicating factors, especially foreign body, obstruction proximally or distally, specific granulomatous disease, and carcinoma. Specific treatment of such complications then become part of the treatment of the associated fistula.

Granted a diagnosis not thus complicated, a program to fit the patient should be planned. Thus we must especially take into account the fluid and electrolyte balance, the state of nutrition, and the condition of the abdominal wall when the patient is first seen. Specifically, it has been found advantageous in our experience to place the patient on a strictly tabulated intake-output chart and to match one for the other in daily fluid balancing, with a positive balance of 1500 to 2000 cc. to provide the kidneys with sufficient fluid for adequate clearance of nitrogenous waste. Rowntree[23] has estimated the total fluid poured into the average human duodenum in each 24 hours to be six to seven liters, or two to three times the total plasma volume. Six to seven liters of fluids daily may be necessary while the fistula is draining copiously. Such drainage should be collected by constant suction, utilizing an inlying pump, or if possible by the patient's own co-operative vigilance and interest in collecting his own secretions. Collected fistula drainage is best re-fed, when this becomes possible, via distal jejunostomy. Meanwhile, it must be replaced by like amounts of normal saline or its equivalent. Experimental duodenal fistulas in dogs by Walters and Bollman[25] show that, in the absence of azotemia, life depends on maintenance of lost gastric (chloride) secretion. Daily blood chlorides must be followed adequately to control electrolyte balance. Biweekly measurements of alkali reserve as measurd by CO_2 combining power are sufficient if the blood chloride level is fairly stable, and the renal function adequate, as measured by repeated N.P.N. determinations.

Protein loss and balance are not so accurately appraised even though plasma protein levels be obtained every second or third day. Reliance must be placed on clinical judgment and known experiences in similar depletion states, such as cancer, active ulcerative colitis, and the severely burned patient. At least one and often two whole blood transfusions daily, with the additional use of the parenteral protein hydrolysates and plasma according to hematocrit, will usually maintain a positive protein balance. Calories provided by carbohydrates in the form of glucose, are utilized for their "protein sparing" action in all intravenous infusions other than whole blood and plasma. These fluids must be infused at a rate commensurate with their utilization, which approximates 30 drops per minute maximum in order to obviate urinary spillage and loss. This is a well-known phenomenon where sugar is concerned, but is well emphasized by Tui, Kuo, Chuachiaco, Rosh, and Mulholland,[24] concerning the amino acids as well. Too rapid infusion of protein hydrolysates will usually precipitate

thermal reactions and vomiting, much amino acid spillage, and loss through the kidneys.

Vitamin intake during the period of active fistula drainage is of paramount importance. Large doses, judged by ordinary standards, are not remiss, and are utilized for the same reasons, and in the same doses that Levenson, *et al.* in Lund's laboratory[16] recommended for the severely burned. These are: ascorbic acid, 1000 mg.; thiamine, 50 mg.; riboflavin, 50 mg.; nicotinic acid, 500 mg.; and liver extract, 2 cc. daily. Abbott and Holden[1] have emphasized the occurrence of hypoprothrombinemia with intestinal fistulas and vitamin K therapy as a measure in its correction or prevention. Especially in the hemorrhagic, digestive duodenal fistulas would such therapy seem to be indicated.

Numerous ingenious methods for the prevention of abdominal wall digestion have been used in the past. These may be grouped according to:

1. Mechanical prevention of contact
   a. Positioning patient upside down on Bradford frame[21] or divided mattress[6]
   b. Constant suction[4, 17]
   c. Continuous bath
   d. Insertion of mechanical occluding buttons[12, 17, 26]
2. Chemical neutralization (10 per cent tannic acid, amphogel, Kaolin[7, 8] Gelucil,[10] "optacid" buffer.[22]
3. Enzyme rivalry, whereby protein other than that of the patient's own body is provided in the form of beef extract, egg white, and dried milk, to compete for and engage the fistulous activated trypsin.

These methods are well outlined by MacNaughton[17] and Ochsner.[19] In our experience, the use of amphogel paste and continuous suction, especially if the patient himself can supervise it, have been most useful to control local digestion. In the advanced, severely depleted patient, whose secretions could not be controlled by less radical measures, the use of the Bradford frame, with the patient in the prone position, proved of great help in our military experience. We are in thorough agreement with Bartlett and Lowell that for a successful outcome it is not so much the methods used, as the thoroughness and constancy with which they are carried out.

Fluid and electrolyte maintenance, and prevention and treatment of tissue digestion are conservative methods which may by themselves lead to closure and cure. They are equally important as ancillary measures in the patient who is to be operated upon. Surgical treatment of duodenal fistula is limited and has, we feel, specific indications. Available surgical procedures include distal feeding jejunostomy, simple excision and closure (transperitoneal or extraperitoneal), gastro-jejunostomy, gastro-jejunostomy with pyloric occlusion, and duodeno-jejunostomy. We do not agree with Hartzell[12] that operation is contraindicated except in fistula with distal obstruction. Certain fistulas without distal obstruction have, in our experience, been benefited by surgery (Case I).

As Colp[5] maintained, conservative measures as outlined will usually suffice by themselves in patients whose fistulous discharge is limited and remains so, and whose strength and nutrition are maintained on such regimen. Among similar patients whose chronic, established, fistula is a mere annoyance from month to month, simple excision and closure, preferably via a retro-peritoneal approach to obviate peritonitis is indicated.[5]

The difficult surgical problem, however, presents itself in the patient who does not have such a relatively benign chronic fistula with a small duodenal opening. It is our opinion that acute, recent, copious inflammatory duodenal fistulas should be operated upon early (as in Case 3), and that this should be limited to a feeding jejunostomy in most cases. We have had no experience with the use of an Einhorn[9] tube through the naso-pharynx, stomach, and duodenum into the jejunum for feeding purposes. It would certainly appear to answer the purpose of nutrition as well as a jejunostomy, and to be more desirable than similar tubes inserted through the fistula itself, the presence of which could only prolong the very fistula one is attempting to close.

If for some reason the patient has not been seen shortly after inception of a massive inflammatory duodenal fistula, surgery is probably best postponed[14] (as in Case 1) until visible nutritional improvement commences as a result of vigorously applied conservative measures. Clinical judgment, daily weighing of the patient demonstrating definite weight gain not associated with edema, positive protein balance, absence of anemia, and normal plasma protein levels will aid in gauging the time for jejunostomy in such a patient. It is too much to expect a jejunostomy of itself to be a life-saving measure; it is rather a nutritional prophylaxis in the early case, and an alimentary rehabilitation in the late case in which the patient has already shown a beginning upward trend in clinical course on conservative measures.

As pointed out by Horsley,[13] when a duodenal fistula follows gastrectomy, a gastro-jejunostomy will already have been made, and nutritional loss will be correspondingly less. This is the "end" type of Bartlett and Lowell,[2] and is translated by them into prognostic terms as follows:

End type, 14 cases, mortality 14 per cent
Lateral type, 114 cases, mortality 40 per cent

Various authors have described other operative procedures, including gastro-enterostomy with and without pyloric occlusion (Berg,[3] and Deaver cited by McGuire[18]), and duodeno-jejunostomy. Berg's two cases have seemed to us atypical in that the first patient had a previous bile-diverting cholecyst-duodenostomy and a carcinoma of the head of the pancreas may have blocked pancreatic secretions. Berg's second patient died the day after operation, and absence of fistula drainage during a single postoperative day could have been as likely due to postoperative gastric retention as proof of cure of the fistula. In any event, gastro-enterostomy with pyloric occlusion does not divert either the bile (500 cc. daily)[11] or pancreatic juice (700 cc. daily)[11] or duodenal secretions. Colp[5] states that gastro-enterostomy is worthless without the pyloric

occlusions, that it does not guarantee closure of the fistula when it *is* combined with pyloric occlusion, and that when so combined it is a shocking procedure associated with an 85 per cent mortality. Kittelson,[14] showing a 35.8 per cent over-all mortality, divided this into 27.7 per cent mortality among 65 conservatively treated duodenal fistulas and a 50 per cent mortality among 30 surgically treated cases; 7 out of 13 died who underwent gastro-enterostomy combined with fistula closure or pyloric occlusion.

The patient's best chance of recovery, it would seem to us, lies in the accurate evaluation of his daily nutritional state, vigorous employment of ancillary conservative measures to correct fluid and chemical imbalance, early jejunostomy if necessary to support the above measures, and local control of the wound irritation. Surgery in the form of direct operative attack with or without shunting procedures should be employed only after it has become apparent that full vigorous use of the conservative measures will not sustain the patient during his usually prolonged period of recovery.

SUMMARY

Massive fluid and electrolyte imbalance, nitrogen retention, and enzymic digestion of the abdominal wall confront the untreated patient with acute inflammatory duodenal fistula. The causes of such fistulas are discussed, the attendant abnormal physiology reviewed, and specific conservative and operative measures are suggested for their management and control. Five illustrative case reports, four of the "lateral" and one of the "end" type, are included, with a discussion of each. The prognostic implication of these two types is emphasized.

CONCLUSIONS

1. Duodenal fistula may follow operations in the right upper quadrant, especially gastrectomy, gallbladder surgery, and difficult right nephrectomy. Traumatic duodenal rupture and perforated duodenal ulcers account for some cases.

2. A distinction is made between post-gastrectomy duodenal stump "blow-out," giving the "end" type duodenal fistula, and the "lateral" type; the former is associated with a 14 per cent mortality, the latter with a 40 per cent mortality. "End" fistulas are associated with gastro-enterostomy at the onset, but the "lateral" type, with bowel continuity preserved, transmits almost the entire upper gastro-intestinal contents to the exterior.

3. Massive fluid and electrolyte replacement, as indicated by daily laboratory and clinical evaluation, is necessary for recent acute inflammatory fistulas. Over six liters daily of normal saline or its equivalent may be required to correct dehydration, alkalosis and uremia.

4. Enzymic tissue digestion by the activated trypsin of duodenal fistula drainage constitutes a serious problem in management. Encouraging results have followed the use of the prone position on a Bradford frame, constant

suction to the wound managed by the patient himself, and local applications of emollient agents.

5. Distal feeding jejunostomy is presented as a nutritional prophylaxis in the early case, and an alimentary rehabilitation in the late case, to be used as a supplement to non-operative measures. It can be of life saving value as in Case 3, with complete rehabilitation of the patient.

6. Major surgical procedures in the form of direct operative attack with or without shunting procedures should be employed only after vigorous supportive measures, with or without jejunostomy, have failed to maintain the nutritional state during the long period necessary for healing of the fistula.

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METABOLIC STUDIES OF AN UNUSUAL CASE OF SURVIVAL FOLLOWING RESECTION OF ALL BUT EIGHTEEN INCHES OF SMALL INTESTINE

COMPLICATED BY COMBINED ABDOMINOPERINEAL RESECTION FOR CARCINOMA OF THE RECTUM PERFORMED NINE YEARS PREVIOUSLY*

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INTRODUCTION

THERE HAVE BEEN occasional isolated case reports of survival after extensive intestinal resection since Koeberle's first report in 1881 (Haymond[17]). However, the emphasis has been on the surgical aspects of these cases, and surprisingly few metabolic studies have been performed on patients who have survived beyond a six-month period. It is generally accepted for purpose of discussion that a massive resection consists of removal of more than 200 cm. of small bowel. More important from a physiologic standpoint would be the length of remaining bowel; and the emphasis should not be so much on the measurement of the excised specimen as on the length of remaining absorptive surface, as this will more accurately reflect the metabolic deficiency.

HISTORICAL

An excellent and detailed review of the literature up to 1912 was first presented by Flint.[13] Again, in 1935, H. E. Haymond critically analyzed and collected 257 cases up to that date.[17] For those interested in the historical background and for detailed protocols, these references will suffice. Since 1935 there have been 13 additional case reports of massive intestinal resection, only one of which had an adequate metabolic investigation.[2, 3, 5-8, 11, 13-16] E. S. West, Todd, *et al.*[27, 28] did repeat nutritional surveys in 1938 and 1940 on a patient with only three feet of remaining small intestine. Their findings were that carbohydrates were utilized normally, proteins were not absorbed well (only 70 to 75 per cent being utilized), and that fat absorption was poor (45 per cent being lost in feces). Also, there was excessive loss of calcium when a large amount of fat was included in the diet. This work represents the sum total of metabolic investigation to date in patients with massive small intestinal resection.

CASE REPORT

On August 1, 1948, Mrs. E. G., a 55-year-old woman, was brought to the University Hospital in a state of shock. Two days before admission she noted the onset of mid-abdominal, cramping pain which radiated to the back and both shoulders. She developed

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progressive anorexia, nausea, vomiting and obstipation. Within a few hours of admission her abdomen became severely distended and she went into circulatory collapse.

Nine years before, an abdominoperineal resection with permanent colostomy was performed for cancer of the rectum. She was re-admitted 3 years ago for profuse bleeding from the colostomy. An exploratory laparotomy was then performed without discovering the source of the bleeding, and aside from the development of a ventral hernia in this wound, her subsequent course was uneventful and she had no recurrence of the bleeding. She maintained weight and remained in fairly good health up to the time of the present illness.

On physical examination she appeared acutely ill, toxic and dehydrated, and was complaining bitterly of abdominal pain. Her temperature was 97, pulse 160, feeble and thready, her blood pressure 90/50 and her respiration 28. There was evidence of severe dehydration, with inelastic dry skin and a dry, coated tongue. There was no icterus. The heart and lungs were negative. The abdomen was markedly distended and tympanitic, and a melon-sized, tense mass protruded through the upper two-thirds of the left rectus scar above a partially prolapsed and edematous end-colostomy. There was diffuse, exquisite, direct and rebound abdominal tenderness and muscle spasm; no peristaltic sounds were audible. Digital examination of the colostomy was negative. Pelvic examination revealed bulging in the cul-de-sac but normal uterus and adnexae. The perineal scar was soft and showed no evidence of recurrence of carcinoma.

FIG. 1.—Artist's drawing of operative findings, (gangrene of entire small intestine except for first 18" of uninvolved jejunum). A. Stomach. B. Duodenum. C. Intact jejunum. D. Permanent colostomy. (Status nine years past combined abdominal perineal resection for carcinoma of the rectum). E. Transverse operative incision. F. Gangrenous small bowel in ventral hernia sac (in bracket).

Laboratory findings on admission were as follows: Flat plate of the abdomen revealed moderately severe ileus, with dilatation of both small and large intestine and a suggestion of peritoneal fluid. Hemoglobin was 16.5 Gm. with 5.6 million red cells and 18,500 white blood cells, with 88 per cent polymorphonuclear leukocytes, 80 per cent nonfilamented. Urine was negative except for a 2-plus acetone and a 1-plus albumin. The hematocrit was 47 volumes per 100; blood carbon dioxide combining power was 33 volumes per 100; blood plasma chloride 102 milliequivalents per liter; blood non-protein nitrogen 29 mg. per 100 cc.; blood sugar 100 mg. per 100 cc. and total protein, 5.7 Gm. per 100 cc.

On admission she received vigorous supportive therapy, including plasma, whole blood and oxygen. Wangensteen drainage obtained several liters of dark brown, malodorous "fecal" fluid. Both penicillin and streptomycin were given preoperatively in adequate doses. After seven hours of this intensive therapy, blood pressure rose to 120/70, pulse slowed to 120 and the patient was considered a suitable risk for laparotomy.

Anesthesia was induced with sodium pentothal followed by nitrous oxide and oxygen, and local infiltration of the wound with one per cent procaine. Her condition was poor throughout the procedure. A long transverse incision was used to gain access to the

ventral hernia sac just above the umbilicus. The wall of the sac was completely necrotic and contained about a liter of foul smelling, brownish fluid. Six feet of completely gangrenous small intestine was strangulated in a ring of fascia 3 inches wide, in which the root of the mesentery had twisted twice on itself as a volvulus (Fig. 1). After division of the fascial ring, and opening into the true peritoneal cavity, a huge amount of similar fluid poured out. The twist of the mesentery had completely infarcted almost the entire remaining small intestine, extending from 18 inches below the ligament of Treitz to 6 inches above the cecum. The proximal 18 inches of jejunum and the entire large intestine up to the colostomy were viable. The mesentery was greatly engorged and hemor-

FIG. 2.—Barium meal four months following operation revealing 18 in. of residual jejunum by actual measurement. A. Stomach. B. Duodenum. C. Ligament of Treitz.

rhagic and all of the vessels appeared to be thrombosed. There was no gross perforation of the infarcted gangrenous intestine, although its wall was paper-thin and necrotic.

In the face of this seemingly hopeless situation no lesser procedure than resection seemed practical. Accordingly, the root of the entire mesentery was quickly divided between clamps and ligated with multiple cotton ties and the entire gangrenous area was resected, using Payr clamps, leaving 18 inches of viable proximal jejunum and 6 inches of distal ileum. The distal end of the ileum was closed in two layers and the end of the jejunum anastomosed to the side of the cecum, using interrupted fine cotton for serosa, and Connell closure with 000 chromic to complete the anastomosis. The entire cavity was then sucked dry and the abdominal wall defect was repaired, using interrupted No. 30

stainless steel wire through fascia and peritoneum after the excess sac was excised. The patient received 1500 cc. of whole blood during the 90 minutes of operating time and left the table in poor condition, her blood pressure 80/40, pulse 140 and showing marked cyanosis. She was immediately placed in an oxygen tent. In the first 36 hours her sole intake consisted of continuous plasma and whole blood infusion, a total of 1000 cc. of plasma and 2500 cc. of whole blood. Other measures included continuous Wangensteen drainage and adequate doses of streptomycin and penicillin. She excreted 900 cc. of urine the first 24 hours, and her general condition slowly responded. Blood pressure rose to 100, pulse slowed to around 100 and her color improved. She had moderate febrile response up to 101 degrees for the first week. Her abdomen never became distended. Her colostomy did not function until the eighth postoperative day, at which time the Wangensteen was first removed. Electrolyte balance was maintained with parenteral fluids for the first week, after which oral feedings were started. Her blood N.P.N. ranged between 25 to 35 mg. per 100 cc.; serum protein 6.2 to 6.8; blood chlorides 95 to 102 milliequivalents per liter; carbon dioxide combining power 40 volumes per 100; prothrombin 95 to 100 per 100.

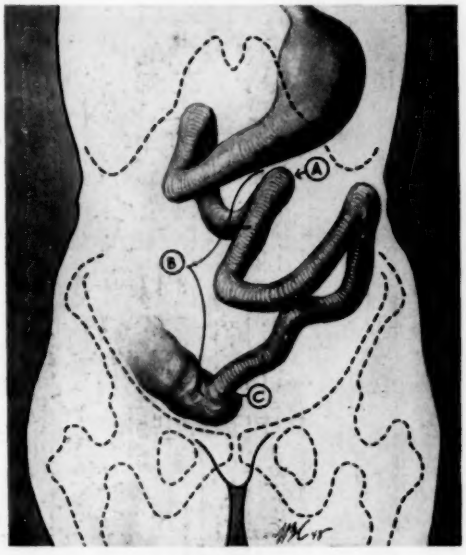

FIG. 3.—Artist's drawing from barium meal roentgenogram. A. Ligament of Treitz. B. Residual 18" of jejunum. C. Jejuno-caecal end-to-side anastomosis.

Despite a moderately severe fascial infection which required irrigation she had fairly good wound healing. On the twelfth and eighteenth postoperative days there were episodes of chest pain with roentgen ray evidence of pulmonary infarction despite absence of clinical evidence of phlebitis in either extremity. Because of the wound complication, ambulation was delayed until the thirty-fourth postoperative day. She was discharged 6 weeks after admission.

The pathologic report was as follows: The specimen consists of approximately 540 cm. of small bowel attached to practically the entire mesentery. The small bowel appears grossly hemorrhagic and necrotic. Cross section of the mesentery reveals thrombosis of nearly every large vessel.

The problem in the hospital once the immediate postoperative critical stage had subsided was the management of the almost continuous liquid discharges from the colostomy. Following any intake of fluid or food by mouth, the patient complained of rather severe but transient cramps, followed by a profuse discharge from the colostomy, varying from a brownish green liquid to a semi-fluid, tape-like stool which kept oozing forth. Drugs to control this and to thicken the stool were for the most part ineffective. They included deodorized tincture of opium, paregoric, bismuth, atropine, belladonna, *Dreft*, psyllium seed derivatives, aluminum hydroxide gel, apple powder and other pectin compounds. A saving grace was the Rutzen bag, which held the liquid discharges quite well (Fig. 4).

When she began oral feedings, the main problem in nutrition was to provide easily assimilated foods, namely glucose and protein hydrolysates fortified with vitamins in adequate doses. The question of volume of food was important, for she tolerated small volumes of food at frequent intervals, but no large meals. Since her return home, she

averages 6 to 8 small feedings a day, with supplements such as glucose, milk, Proteinal,* vitamins and calcium, but she does not require parenteral medication. Fats, apparently being poorly tolerated and absorbed, are held to a minimum. On this regimen her caloric intake is maintained at about 2000 to 2500 calories a day.

Aside from a smooth, somewhat shiny, red tongue, she never demonstrated evidence of gross vitamin deficiency, and her blood counts never showed significant anemia or abnormality in the blood cells. Repeated blood studies at monthly intervals show normal blood count and blood protein level. A gastro-intestinal series performed several months after discharge revealed a very small residual segment of small intestine (measured on the film as 18 inches) with only moderate dilatation of this loop. The site of anastomosis was open. The barium very rapidly progressed to its exit at the colostomy (Figs. 2 and 3).

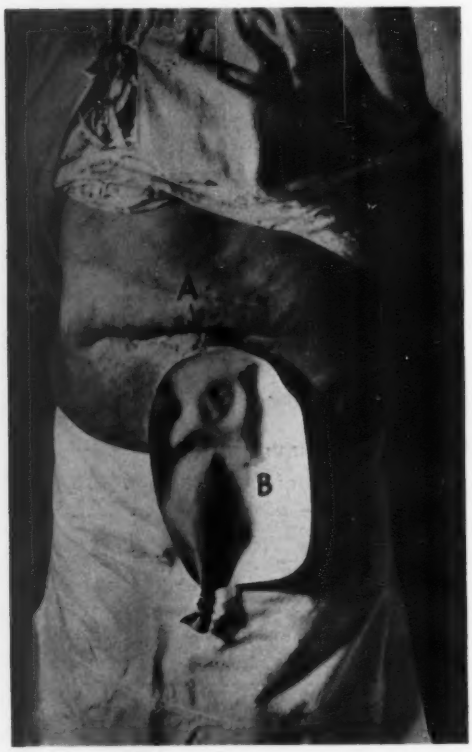

FIG. 4.—Photograph of patient—present status. A. Transverse incision at site of exploration. B. Rutzen bag over colostomy.

Despite an anticipated sharp weight loss and progressive cachexia, the patient did not deteriorate seriously. Her weight slowly fell from her usual 120 pounds prior to this admission to the present 100 pounds, which she maintains. Since her return to her home the patient has been able to do light household duties. Her chief disability lies in the almost continuous colostomy discharge, as many as 15 to 20 movements a day. Her skin and muscle turgor remain good and her general appearance belies the fact that she has only 18 inches of residual small intestine. At the outset it was inconceivable to us that she could obtain sufficient absorption in this segment to sustain life, let alone nutrition.

In an effort to explain the maintenance of an adequate nutritional state in the face of this gross intestinal deficiency, the patient was admitted to University Hospital in January, 1949, for special studies to determine the absorption and excretion of nitrogen and fat and to determine sugar tolerance.

PROCEDURE

To avoid any marked variation from day to day, the metabolic study period lasted three days, and an average daily value was obtained. The diet used for the study was made to approximate, in so far as possible, the patient's own diet. An attempt was made by the dietitian to follow as closely as possible the

* Proteinal supplied by National Drug Co., Philadelphia, Pa.

eating habits and food desires of the patient. A sample of a 24-hour diet given her is shown below.

SAMPLE DIET FOR A 24-HOUR PERIOD.

Item	Grams	Calories
Eggs (4)	...	316
Butter	30	292
Bread (4 slices)	80	216
Sugar, white	45	180
Cream, light	120	241
Cream of wheat	20	71
Grapefruit juice (sweetened)	100	67
Baked potato	100	85
Beef, ground	85	137
Cottage cheese	100	101
Canned salmon	50	138
Canned pears	100	75
Boiled milk	540	369
Chocolate milk	180	66
Hershey bar	43	239
Whiskey	84	258
Coffee	150	...
Tea	300	...
Total	2127	2851

The patient was encouraged to eat as much of her diet as possible. A sample control diet was prepared with each meal served, and one-half of each item in each meal was preserved for analysis. (This included one-half of all supplementary foods also.) All food left uneaten at each meal was also saved. In the laboratory, all these specimens, the control diet, the uneaten food and the stools (which were marked at the beginning and end of the metabolic period with charcoal ingested with the first and last meal) were emulsified in a Waring blender, using distilled water for quantitative transfer from special collection pots used for this study. They were then placed in separate, known-weight containers, refrigerated and stored for analysis at the completion of the metabolic period.

All urine specimens during this same period were also collected, preserved with hydrochloric acid to prevent loss of ammonia and refrigerated for Kjeldahl analysis.

Upon calculation from food tables (5, 18), the diet served (Table I) contained 224 Gm. of carbohydrates, 105 Gm. of protein (16.8 Gm. of N) and 108 Gm. of fat, with a calculated caloric value of 2633 calories as a daily average.

METHODS

Nitrogen of the dietary elements, stools and urine specimens was determined by the Kjeldahl procedure, using the digestion method of Campbell and Hanna[7] and the titration method of Meeker and Wagner.[20] Every precaution was followed to avoid loss of nitrogen from the stool and urine specimens, as

well as the food specimens. These were immediately analyzed for nitrogen on completion of the collection.

To determine the total solids or dry matter of the specimens—the control diet, the uneaten diet, and the stools—a conversion factor was determined. Quadruplicate 10 cc. samples of the well mixed semi-liquid, emulsified media

TABLE I.—*Control Diet Calculated and Analyzed.*

	Calculated		Analyzed		Per Cent of
	72 Hr.	Ave. 24 Hr.	72 Hr.	Ave. 24 Hr.	Calculated
Carbohydrates.....	671 Gm.	224 Gm.	(671)*	(224)*	.....
Proteins.....	315 Gm.	105 Gm.	295.8 Gm.	98.6 Gm.	93.9%
As nitrogen.....	50.4 Gm.	16.8 Gm.	47.3 Gm.	15.8 Gm.	.....
Fats.....	325 Gm.	108 Gm.	296.6 Gm.	98.9 Gm.	91.3%
Calories.....	7900	2633	6541.5	2180.5	82.8%

*Calculated.

were weighed in weighing bottles in the wet state and then dried to constant weight. The conversion factor (dry weight/wet weight) was then applied to the known total wet weight of each specimen.

Fowweather's[15] modification of Saxon's[26] method, a wet extraction method,[24] was then used on aliquots of known volume (10 cc.) and weight of the food specimens and the feces. This method gave, by fractionation, a measure of the total lipoid concentrations and the relative proportions of the

TABLE II.—*Nitrogen Metabolism—Detailed.*

	72 Hour		Ave. 24 Hours		Per Cent of
	As Protein	As Nitrogen	As Protein	As Nitrogen	N—Intake
Intake:					
Diet eaten.....	207.1 Gm.	33.1 Gm.	69.0 Gm.	11.1 Gm.	.....
Output:					
Stools.....	90.1 Gm.	14.4 Gm.	30.0 Gm.	4.8 Gm.	43.2%
Urine.....	115.0 Gm.	18.4 Gm.	38.3 Gm.	6.2 Gm.	55.9%
Total.....	205.1 Gm.	32.8 Gm.	68.3 Gm.	11.0 Gm.	99.1%
Balance:					
Intake.....					
Output.....	+2.0 Gm.	+.3 Gm.	+.7 Gm.	+.1 Gm.	.....

free fatty acid, the soaps and the neutral fats in these specimens. The method was standardized by running recoveries on oleic acid.

The oral glucose tolerance test consisted of giving the patient orally a dose of 100 Gm. of glucose in 400 cc. of water flavored with lemon juice. The blood specimens were drawn at fasting, one-half, one, two, three, and four-hour intervals. The blood sugar concentrations were determined by the method of Folin and Wu.[14] Her carbohydrate intake prior to the test was not excessive.

* Normal fecal nitrogen output equals approximately one-tenth of the daily ingested N on a normal intake; 1 to 2 Gm. N with an average of 1.3 Gm.[23]

RESULTS

Nitrogen Metabolism: *Nitrogen intake:* Detailed data for the total nitrogen intake is summarized in Table II. The average daily value was found to be 69.0 Gm. of protein or 11.1 Gm. of nitrogen. *Nitrogen output:* In Table II the total average daily output was found to be equivalent to 68.3 Gm. of protein or 11.0 Gm. of nitrogen, of which 4.8 Gm. of N (43.2 per cent of the total N intake), occurred in the stools and 6.2 Gm. of N (55.9 per cent) occurred in the urine. As a rule, fecal nitrogen output will approximate 10 per cent on normal intake or an average of 1.3 Gm. of N of the total nitrogen ingested.[23]* *Nitrogen balance:* The total output of N came to 99.1 per cent of the intake. The patient is probably in nitrogen equilibrium on this diet, rather than in slightly positive balance (Table II and Fig. 5).

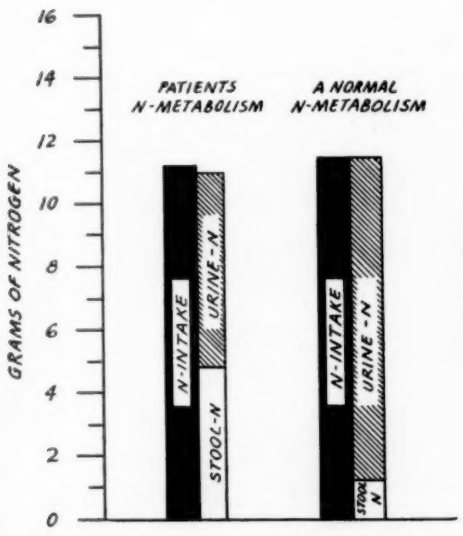

FIG. 5.—Nitrogen Metabolism (as Protein)

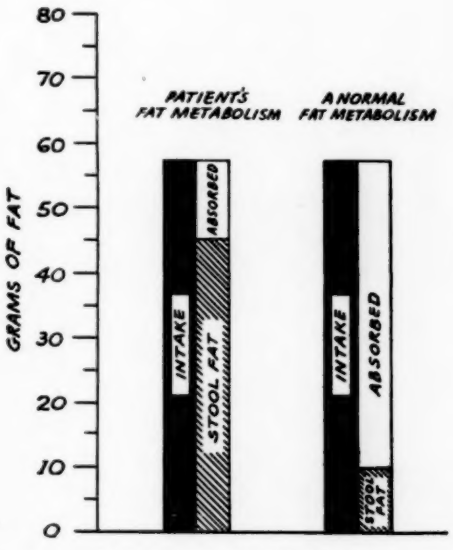

FIG. 6.—Fat Metabolism

Fat Metabolism: An inspection of Table III, which gives summarized detailed data on the fat study results, shows that with a daily fat intake of 58.5 Gm. daily fat absorption was 13.2 Gm., or 22.5 per cent of that ingested; while 77.5 per cent, or 45.3 Gm., was lost in the stools (Fig. 6). It has been found that a normal adult on an ordinary mixed diet utilizes approximately 90 per cent of the fat ingested, losing in the feces, from 5 to 10 per cent.[23]

Partition of the total fats of the specimens analyzed are also shown in Table III. The daily total dry matter of the feces was 106 Gm., of which 42.8 per cent, or 45.3 Gm., was total fat, and free fatty acids were 31.3 per cent, or 33.2 Gm. of the dry matter. It is readily apparent that the daily excretion of free fatty acids is very high, amounting to 73.3 per cent of the total fat output of the stools. The relative proportions of fats as soaps and neutral fat

TABLE III.—*Fat Metabolism—Intake, Excretion, and Absorption with Partition of Fats—24-Hour Average Values.*

Analyzed Specimens	Total Dry Weight Grams	Total Fats			Free Fatty Acids			Soaps			Neutral Fats		
		Per Cent			Per Cent			Per Cent			Per Cent		
		Grams	Dry Matter	Total Fat Ingested	Grams	Dry Matter	Total Fat of Specimen	Grams	Dry Matter	Total Fat of Specimen	Grams	Dry Matter	Total Fat of Specimen
Control diet	459.6	98.9	21.5%	.....	3.7	.8%	.....	...	.....	.....	95.1	20.7%	.....
Diet uneaten	156.2	40.4	25.9%	.....	1.6	1.0%	.....	...	.....	.....	38.8	24.8%	.....
Intake diet eaten	303.4	58.5	19.3%	.....	2.1	.7%	3.6%	...	.....	.....	56.3	18.6%	96.2%
Output stools (excreted)	106.0	45.3	42.8%	77.5%	33.2	31.3%	73.3%	3.3	3.1%	7.3%	8.8	8.3%	19.4%
Balance intake—output (absorbed)		13.2		22.5%									

and their percentage of the dry matter and of the total fat output are shown in this table. These fall into a normal range, as shown by comparison with Table IV, a study by Fowweather[15, 23] of fat partition in the stools of normal adults (84 cases). This patient, with only 18 inches of small intestine, demonstrates abnormal excretion of total fat and free fatty acids, whereas excretion of combined fatty acids as soaps and neutral fat fall within a normal range.

Oral Glucose Tolerance: The results of the oral glucose tolerance test are shown by the curve in Figure 7. With a fasting blood sugar of 95 mg. per 100 cc. (a very faint trace of sugar was found in the fasting urine specimen), the curve seems to be a normal one with a peak of 130 mg. per 100 cc. reached in a half hour and descending to the fasting level in two hours.

Caloric Intake: Actual analysis of the protein and fat content of the control diet showed 98.6 Gm. of protein (15.8 Gm. of N) which was 93.9 per cent of that calculated by the dietitian (Table I) and the fat content was 98.9 Gm., which was 91.3 per cent. The estimated caloric value of the analyzed control diet, assuming the carbohydrate to be the same as in the calculated diet, was therefore about 2180.5 calories (82.8 per cent) instead of 2633 calories, as originally calculated (Table I).

However, actual intake, when the uneaten food was analyzed, and proper subtractions made from the control diet, was 69.0 Gm. of protein (11.1 Gm. of N) and 58.5 Gm. of fat as a daily average. Her daily caloric intake was about 1506 calories (Table V).

DISCUSSION

In evaluating the physiologic effect of extensive resection of the small intestine, one must keep in mind the difference between marginal survival and a nearly normal nutri-

tional status. With certain other organs, such as the kidney, liver and pancreas, the minimum necessary for survival has been fairly well established. Yet as concerns the small intestine, despite probably inaccurate estimates (such as 50 per cent being necessary for normal survival),[13] no critical evaluation has been made. Again, it must be stressed that an underlying disease process which had necessitated a massive resection, *i.e.*, regional ileitis, cancer, etc., would compound the deficiency of the resection *per se*.

The absorption of all the essential nutrients is practically completed in the small intestine. The single chief problem posed by massive small intestinal

TABLE IV.—*Partition of Fat in Normal Human Stools.*[15, 23]
Dry Matter 4.6 to 38 Per Cent (Average 20 Per Cent) of Total Weight of Stool.

Of This	Per Cent of Total Dry Matter		
	Minimum	Maximum	Average
Total fat	7.3	28	17.5
Soaps	0.5	11	4.6
Free fatty acid	1.0	10	5.5
Neutral fat	2.5	12	7.3

resection is, therefore, that of absorption, not only as regards surface for absorption but also as regards what might be called time-contact relationships between food, mucosa and ferments. The presence of intact, normal gastric and duodenal secretions, including pancreatic and hepatic enzymes, should assure a normal digestion potential. This has been shown to be the case both experimentally (Grey, *et al.*,[16]) and clinically (Todd, Elman, *et al.*,[27, 11]).

As far back as 1896 Monari[13] postulated from experimental work on dogs that hypertrophy of remaining small intestine occurs in cases of massive re-

TABLE V.—*Determination of Caloric Intake Average 24-Hour Values.*

Control Diet		Diet Uneaten	Intake
Total Dry Weight*, grams	459.6	156.2	303.4
Total fats*, Grams	98.9	40.4	58.5
Per cent of dry weight	21.5%	25.9%	19.3%
Total protein*, Grams	98.6	29.6	69.0
Per cent of dry weight	21.4%	18.9%	22.7%
Carbohydrates, Grams	262.1	86.2	175.9
Per cent of dry weight	57.0%	55.2%	58.0%
Total calories	2332.9	826.8	1506.1

* All analyzed except carbohydrates and calories, which were estimated on the basis of dry weight. Factors used for obtaining calories were fats—9, proteins—4, and carbohydrates—4.

section. This was supported by microscopic evidence of thickening of the mucosa and by actual increase in the number and size of the villi. This important observation was later confirmed by Evans and Brenizier[12] and Flint.[13] However, there has been no comparable demonstration in the human being, as shown by autopsy findings.[6] This whole subject of compensatory phenomena in the intestinal tract following massive resections is in need of investigation, and better postmortem follow-up.

Despite the very rapid progress of food through this patient's abbreviated intestinal tract, she has maintained a nitrogen balance, even though she absorbs only slightly over half of the nitrogen ingested. With digestion accomplished by the intact enzyme system, she apparently absorbs enough protein from 18 inches of jejunum to maintain balance.

The fat studies in this case agree with previous work[13, 27, 28] demonstrating that these patients are unable to absorb fat to any great degree. The fat partition studies show a normal ability to hydrolyze fats, the key defect being in absorption. A striking observation in this case was the high percentage of free fatty acids, amounting to 73 per cent of the total fat output of the stools, while soaps and neutral fats were normal. This might explain the maintenance in this case of normal serum calcium level and the absence of tetany, since there was no undue excretion of calcium as soaps.

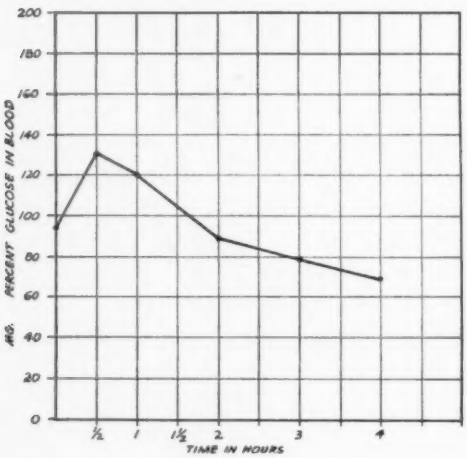

FIG. 7.—Oral glucose tolerance test curve of patient.

The glucose tolerance test, which was surprisingly normal (Fig. 7), substantiates the concept of Peters and Van Slyke[23] in interpretation of a sugar tolerance curve. According to them, it is only the initial part of the ascending limb of the curve which is attributable directly to the absorption of sugar from the alimentary canal. For less than 30 minutes the speed with which the blood sugar of a normal person rises parallels the rate at which glucose is absorbed in the intestine, and after this, utilization is so greatly accelerated that it dominates all other influences in the determination of the form of the curve. Hence, the sensitivity of the oral glucose tolerance test depends only on normal functioning of the upper portion of the digestive system, which this patient has.

Thus, the studies bear out previous concepts in relation to the feeding of patients with massive intestinal resection; *i.e.*, fat is poorly tolerated and absorbed and should be restricted; proteins should be given in easily absorbable form and in adequate amounts. Carbohydrates should be given at frequent intervals. The feeding process must be almost a continuous one throughout the day to utilize the absorptive capacity of the remaining segment of small intestine to its fullest.

SUMMARY AND CONCLUSIONS

1. A metabolic study has been carried out involving determinations of total dry matter, nitrogen and fat intake, nitrogen and fat output and a glucose tolerance curve on a 55-year-old woman surviving 12 months in fair nutrition

following resection of all but 18 inches of her small intestine (a status further complicated by a previous abdominoperineal resection for cancer of the rectum). The case report is included.

2. Hydrolysis of fat is within normal limits, but absorption is limited.

3. This patient maintained nitrogen equilibrium, although only little more than half of the nitrogen intake was absorbed.

4. A normal glucose tolerance curve was obtained and interpreted in the light of present knowledge.

5. An optimal diet in cases of massive small intestine resection should be high in carbohydrate and easily assimilated protein, low in fat, and low in residue. It should be given in small, frequent feedings with adequate supplementary vitamins.

6. Intractable diarrhea unresponsive to all therapy with drugs, as indicated in this report, presents the single, most distressing problem in these cases.

7. Further metabolic and postmortem studies are indicated to determine the compensatory phenomena which might account for survival following massive intestinal resection.

Appreciation is expressed for invaluable interest and advice given by Dr. Richard H. Lyons, Professor of Medicine, Syracuse University.

ADDENDUM

In May, 1949, the patient was admitted to Mt. Sinai Hospital, New York City, for further metabolic study under the direction of Drs. I. Snapper and Adlersberg, who will publish their results at a later date.

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BLADDER RECONSTRUCTION FROM CECUM AND ASCENDING COLON FOLLOWING RESECTION OF PELVIC VISCERA*

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THE CONSTRUCTION of a blind pouch of intestinal tract to serve as an artificial urinary bladder is not a new procedure. Hinman and Weyrauch in 1936[1] reviewed the many ingenious arrangements of uretero-intestinal anastomosis that have been used. We first resurrected one of these procedures in 1940 and 1941 at the Ellis Fischel State Cancer Hospital in Columbia, Missouri. An isolated segment of sigmoid colon draining through an abdominal stoma was used as a receptacle for the ureters following pelvic evisceration for three cases of far-advanced carcinoma of the prostate without metastases and one of carcinoma of the bladder. There was a 50 per cent operative mortality. Since the end of the war we have switched our attention to cases of far-advanced carcinoma of the rectum and sigmoid as being a lesion better suited pathologically to radical surgery. However, this lesion usually requires such extensive resection of the sigmoid colon that use of the latter as a receptacle for the urine is impractical. It is the purpose of this paper to report the use of terminal ileum and ascending colon as a pouch for the reception of the ureters following pelvic evisceration for carcinoma of the rectum and sigmoid involving the trigone of the bladder.

Verhoogan[2] in 1908 was the first to transplant ureters into an isolated segment of terminal ileum and ascending colon, using an appendicostomy as an urethra. He reported this procedure in two cases requiring total cystectomy for carcinoma of the bladder. Neither patient survived the immediate postoperative period. Makkas[3] in 1910 reported two successful cases of exstrophy of the bladder in which an artificial bladder was constructed according to this technic. In order to obviate the likelihood of fecal soilage of the ureteral stomata, he staged the procedure so that a month intervened between the isolation of the pouch from the intestinal stream and the ureteral implantation. His results were strikingly successful. Lengemann[4, 5] in 1912 reported 12 cases in which he created an artificial bladder in patients with exstrophy of the bladder or with bladder carcinoma. It was his belief that anastomoses so constructed would remove the threat of urinary tract infection. His operative mortality was 66 per cent in this early series.

Because of the forbidding mortality as reported by authors some 35 years ago, the construction of artificial bladders from isolated loops of intestine fell into disuse. In 1922 Hinman and Belt[6] proved experimentally that when the

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total urinary excretion is poured into the duodenum the animal dies within 12 days, with retention of nitrogenous substances in the blood. This impressive finding has led to uncertainty as to the safety of implanting ureters into the terminal ileum or right colon. However, the hazard of nitrogenous absorption from the right colon was minimized by Turner and Saint[7] in 1935, who demonstrated that after the ordinary uretero-sigmoidal anastomosis, the entire large bowel acted as a reservoir for urine in four of six cases studied. It is only through the extension of surgery to certain far-advanced carcinomas of the rectum that the necessity of deliberately subjecting the right colon to urinary retention has arisen.

Because of advances in surgery and its allied sciences the modern surgeon is now limited in performing massive visceral resections only by physiologic and anatomical boundaries beyond which it is impossible to accomplish reconstruction that will leave the patient in a state compatible with a comfortable existence. Pelvic evisceration is a procedure that may have a wide application in the treatment of malignant disease, provided it can be demonstrated that satisfactory reconstruction can be done on an acceptable percentage of cases. Carcinoma arising in the rectum or sigmoid and without remote metastases presents one of the most favorable lesions for this type of massive resection. Dixon and Benson[8] have reported results of partial cystectomy in a group of 40 patients found to have involvement of the dome or posterior bladder wall by carcinoma of the sigmoid. The chances for cure or palliation may be just as good if the lesion involves the trigone of the bladder. However, in such a case, it becomes necessary to remove the bladder and prostate with the rectum if the lesion is to be circumscribed. For obvious anatomical reasons, as indicated by Dixon, lesions with this complication are usually confined to males. However, involvement of the trigone in females is possible through extensive invasion of the vagina or through recurrent tumor (Case 2). Two cases are here reported in which the terminal ileum and cecum respectively were used as a receptacle for the ureters after pelvic eviscerations.

CASE REPORTS

Case 1.—J. M., 68-year-old white man was subjected on July 5, 1947, to an abdominoperineal resection of a very large rectal carcinoma. It was recognized preoperatively by cystoscopic examination that cystectomy would be required if the entire mass were to be removed, although there was no ureteral obstruction. Resection of the urinary bladder, seminal vesicles, and prostate en bloc with the rectum was carried out. The procedure was greatly facilitated by bilateral ligation of the hypogastric arteries. A left lower quadrant colostomy was made. The ureters were then implanted obliquely into the terminal ileum, the ureteral catheters being drawn through the ileocecal valve and out a right lower quadrant cecostomy (Fig. 1). Fourteen days postoperatively the patient was discharged, having had an uneventful hospital course. He drained only small amounts of urine from the cecostomy, the remainder of the urine passing from the colostomy in the left lower quadrant. On admission, the patient's NPN was 17 mg. per 100 cc. Immediately following operation the level went up to 33 mg. per 100 cc. At discharge it had subsided again to normal.

Study of the specimen removed at operation revealed the muscularis of the bladder to be invaded. The tumor cells were arranged in dense bundles and there was diffuse infiltration of connective tissue without gland formation. Only the adjacent lymph nodes contained metastases.

On August 17, 1947, the patient was readmitted for isolation of the terminal ileum and ascending colon. Several days prior to admission he had experienced an episode of abdominal pain with nausea and vomiting. At this time there was a slowing up of the bowel movements which had been numbering 10 to 15 per day. Partial intestinal obstruction was suspected but the symptoms disappeared completely shortly after admission to the hospital. The NPN on admission was 50 mg. per 100 cc., but subsided promptly on hydration.

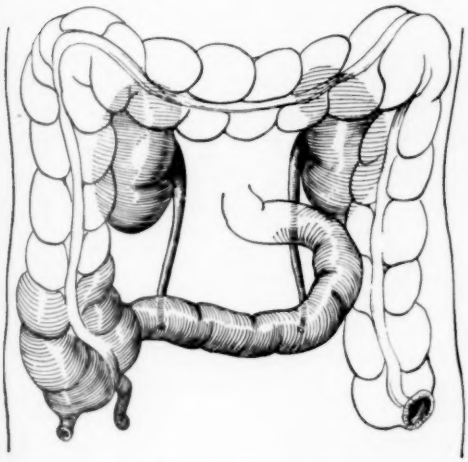

FIG. 1.—(Case 1.) Ureters implanted into terminal ileum. This was done by "tunneling" the ureters through the bowel wall, a practice since discarded. A cecostomy was made for future drainage of the isolated pouch. The appendix was atrophic and not removed.

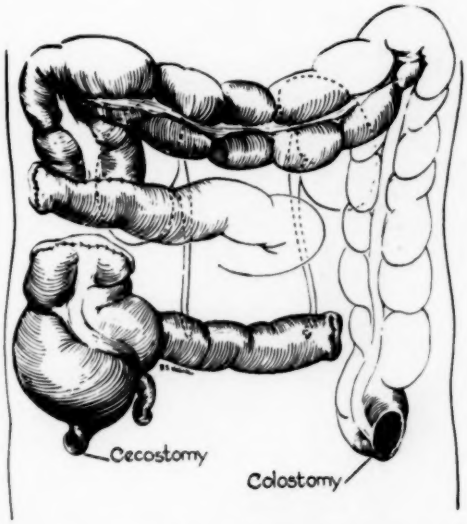

FIG. 2.—(Case 1.) Anastomosis of terminal ileum to ascending colon with isolation of terminal ileum and cecum.

On August 28, 1947, a second stage procedure was done. A blind loop of intestine was isolated, using the terminal ileum and a part of the ascending colon. Both ends of this segment were closed and the continuity of the bowel was re-established by anastomosing the proximal end of the ileum to the ascending colon (Fig. 2). As soon as the urinary stream was thus diverted from the intestinal tract, the colostomy came easily under control, moving only once or twice daily, much to the relief of the patient and his family. Upon discharge from the hospital the urinary stream drained through a catheter placed through the cecostomy opening. The urine was clear and the patient was afebrile. The NPN on discharge was 17 mg. per 100 cc.

On October 19, 1947, the patient was re-admitted to the hospital because of chills and fever. It was obvious that an ascending urinary infection was present. A catheter was placed in the cecal pouch for continuous drainage and penicillin therapy was instituted. The infection came under control rapidly. The highest NPN on this admission was 33 mg. per 100 cc. and the lowest 21 mg. per 100 cc. Pyelograms (Fig. 3) showed moderate hydronephrosis. Fig. 4 shows the pouch injected with opaque solution.

At the present time (July, 1949) the patient is quite well. He takes daily trips by automobile and is up and around the house and yard a good part of each day. His appetite

is good. He has never learned to regulate his colostomy perfectly, having refused to take a regular morning enema. As a consequence he occasionally becomes constipated, following which he may have several bowel movements in one day. There has never been diarrhea or any colon reaction that might be attributed to the fact that the cecum is being used as a urinary reservoir. The NPN on January 6, 1949, was reported as 42 mg. per 100 cc. by the patient's local physician. A catheter is worn in the cecostomy tract continuously (Fig. 5). The cecal pouch is drained intermittently during the day and the catheter is connected to a bedside bottle at night. There is no evidence of recurrent carcinoma in the abdomen or perineum.

FIG. 3

FIG. 4

FIG. 3.—(Case 1.) Pyelograms three months following implantation of ureters into terminal ileum.

FIG. 4.—(Case 1.) Cecal pouch injected with opaque solution.

Comment. It was originally felt that this procedure would not be justified unless the patient could be made continent of urine. A colostomy plus two skin ureterostomies was considered as being incompatible with a comfortable existence. It was doubted that a single abdominal cloacal opening would be much better, and this opinion was borne out by the distress suffered by the patient and his entire family during the period that the ureters emptied into the intact bowel. Providing an isolated intra-abdominal receptacle for the urine with a single external stoma subject to some method of control was thought to be the only solution. The indwelling catheter in the cecostomy tract in this case has been satisfactory.

This patient has moderate hydronephrosis which is thought to be due to the method of oblique uretero-intestinal anastomosis. The NPN determination of January 6, 1949, was done elsewhere and compares to a level of between 28

and 33 mg. per 100 cc. at our own laboratory. This represents a slight elevation of NPN and in the presence of hydronephrosis we are inclined to attribute it to decreased renal function. It is of interest in this case that there has been but one episode of clinically evident urinary infection. Recent uretero-enterostomies have been done by direct implantation of the ureter through the bowel wall with mucosa-to-mucosa suture.[9] Since adopting this method the incidence of dilatation of the ureter and kidney pelvis has decreased.

There has been no evidence that subjecting this amount of ileum and ascending colon to urinary retention has had a deleterious effect on this patient.

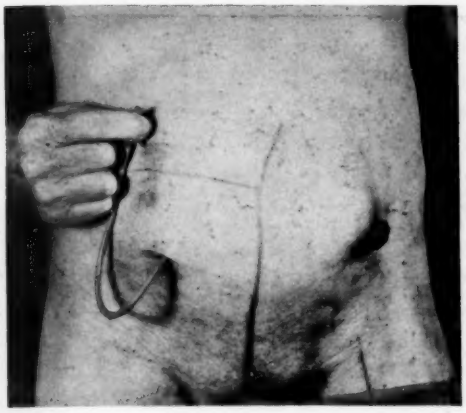

FIG. 5.—(Case 1.) This patient wears a catheter through the cecostomy tract continuously. The catheter is drained at intervals during the day and connected to a bottle at night. The tight cecostomy tract prevents leakage.

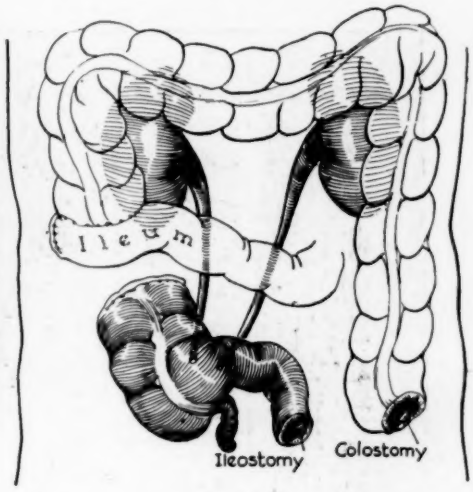

FIG. 6.—(Case 2.) Ureters implanted into cecum and terminal ileum brought out for drainage of urine.

Case 2.—N. R. M., a 48-year-old housewife, was admitted to Barnes Hospital on July 3, 1946, with a one-year history of increasing constipation. Physical examination revealed a large rectal mass involving the anterior rectal wall, the recto-vaginal septum and bulging into the vagina. There was no lateral fixation of the tumor. Biopsy revealed mucoid carcinoma.

On July 8, 1946, an abdominoperineal resection was done. In order to circumscribe the mass a complete hysterectomy with excision of all but a small portion of the anterior vaginal wall was necessary. This portion of the vagina was left in order not to interfere with function of the urethra. A left lower quadrant colostomy was made.

The operative specimen revealed a massive carcinoma of the mucoid type without demonstrable local metastases. The vaginal wall was invaded by the tumor. The resection appeared to have been complete.

The postoperative course was uneventful. The perineal defect that could not be closed healed slowly by secondary intention. For 22 months the patient remained well and led a normal life.

On May 7, 1948, the patient was re-admitted to the hospital. Two weeks prior to this date she had developed difficulty in emptying her bladder. Examination revealed a recurrence of mucoid carcinoma in the small remaining segment of anterior wall of the vagina. The patient was in excellent general condition. There was no evidence of dis-

tant metastases. The recurrent tumor was confined to the region of the urethra and bladder trigone and it was felt that resection was possible.

On May 15, 1948, a second operation was performed through an abdominal approach. The bladder, urethra, vulva, and perineal floor were resected, the anterior plane of dissection being accomplished with the actual cautery beneath the periosteum of the pubic rami and symphysis. The ureters were implanted into the cecum, which was rotated toward the midline as shown in Figure 6. The ileum and ascending colon were sectioned, the proximal ileum then being anastomosed to the ascending colon and the distal ileum being brought out through the abdominal wall for the drainage of urine. Since there was no peritoneum left below the level of the iliac vessels it was necessary to resort to gauze packing in the lesser pelvis to support the intestines. Six two-inch vaginal packs were used for this purpose. It was impossible to close the external perineal wound.

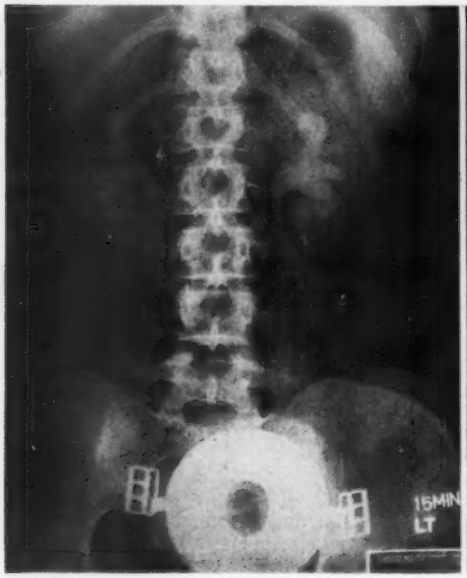

FIG. 7 FIG. 8

FIG. 7.—(Case 2.) Pyelograms five months after implantation of ureters into cecum.
FIG. 8.—(Case 2.) Cecal pouch injected with opaque solution.

The surgical specimen revealed the urethra to be completely encircled by mucoid carcinoma which extended up into the bladder. There were no lymph nodes with the specimen.

The postoperative course was surprisingly smooth. The urine drained freely through a catheter placed in the ileostomy. The perineal packs were changed first on the sixth postoperative day. Only five gauze packs were re-inserted. Subsequently, when the pack was changed, less and less gauze was re-inserted, thus allowing the intestines to descend into the pelvis and obliterate the enormous defect. The NPN was elevated to 31 mg. per 100 cc. 2 days following the operation. Two weeks later the NPN was down to 17 mg. per 100 cc.

The patient was discharged from the hospital on the twenty-fifth postoperative day. Two months later a Rutzen bag was provided as a container for the urine which drains from the ileostomy. The bag worked admirably and the patient has been able to keep dry from that time on. She changes the bag once daily.

On October 18, 1948, the patient was re-admitted to the hospital because of chills and fever of 2 days duration. The symptoms were found to be due to urinary infection, which subsided promptly on sulfadiazine and penicillin therapy. The NPN was reported as 16 mg. per 100 cc. Urine culture grew a heavy growth of coliform organisms before therapy. At the time of this admission the perineal wound was almost completely healed. There was no bare bone. Smooth clean granulations lined the remaining cavity which measured about 2 by 3 cm. Pyelograms and a "cystogram" were made at this admission (Figs. 7 and 8).

The patient was last seen on June 15, 1949. She has had no recurrence of chills and fever. She was in excellent health, doing her housework, and maintaining normal weight. The colostomy moves once daily with a small tap water enema. The perineal defect was completely healed.

Comment. This patient's youth and vigor, plus the fact that she had a mucoid carcinoma, made her a much better subject for salvage than the first case cited. It is doubtful that completion of the entire procedure, i.e., resection, ureteral transplantation, and isolation of the intestinal segment, will often be possible at one sitting. At the time of the operation it was technically preferable to bring the terminal ileum out through the left lower quadrant. This was unfortunate, since it is inconvenient to have the Rutzen bag so near the colostomy. The fact that there is so little dilatation of the ureters and kidney pelves is attributed to the technic of anastomosis.

DISCUSSION

We believe that the construction of a substitute urinary bladder by ureteral implantation into an isolated segment of ascending colon may have a place in the armamentarium of the surgeon doing colon and rectal surgery. It is true that the rectal and sigmoidal lesions to which the procedure will be applicable are few. However, it is considered to be of some importance to know that complete pelvic evisceration can be done and the patient live comfortably thereafter. It also seems that by extending the boundaries of surgery in the treatment of this type of lesion there will be fewer of the less extensive lesions considered inoperable. This is one neoplasm with which the inclination of the surgeon to be radical may be freely indulged. The radiotherapist has retired from the field and raises no objection. The radical procedure has the blessing of the surgical pathologist as long as the specimen shows the lesion to have been grossly circumscribed. So far there is no hormonal or chemical therapy that can be expected to be effective in controlling colon and rectal carcinoma. The patient is doomed without surgery.

Absolute local indications of inoperability of rectal and sigmoidal lesions under the philosophy described above become hard to define. However, lateral infiltration into perirectal fat and into the levator muscles is, in our experience, impossible to circumscribe satisfactorily regardless of how radically inclined one may be. Unfortunately, lateral spread can often not be ascertained with certainty until the time of resection.

Ascending urinary tract infection would seem to be less likely in these cases in which the implanted ureters are isolated from the fecal stream. However, we have no proof that this is so. Although the urine has become grossly clear

except for intestinal mucous shreds, it is quite certain that some organisms persist. Detailed bacteriologic studies and studies on absorption of urea from these pouches will be the subject of a future presentation.

While studying these cases postoperatively it was learned that Gross, Swann and Swenson[10] at the Boston Children's Hospital in treating urinary incontinence in children with myelomeningocele had constructed artificial bladders of isolated sigmoidal loops. More than ten patients have been so treated, with results considered to be very promising. Their method differs from that herein described in that they are able to utilize the sigmoid as a urinary pouch.

SUMMARY

1. The procedure of ureteral transplantation to the terminal ileum and cecum and construction of a blind cecal pouch to act as a urinary reservoir is re-introduced. The procedure is considered to have application in the radical surgical treatment of certain advanced rectal and sigmoidal lesions in which the urinary bladder is involved.

2. Two cases in which the cecum was used as a urinary receptacle after radical resection of the rectum, sigmoid, and bladder are briefly discussed. These patients are alive and well and without evidence of tumor two years and one year after the resection. In each case the functional result is considered to be satisfactory.

Appreciation is expressed to Dr. G. L. Watkins, Sr., and to Dr. Richard Crouch, both of Farmington, Missouri, for their assistance in following the two cases reported.

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UROLOGIC INVALIDISM FOLLOWING ABDOMINOPERINEAL RECTOSIGMOIDECTOMY*

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RESIDUAL ABNORMALITIES in bladder function, injuries to and tumor invasion of the urinary tract frequently account for prolonged invalidism following an otherwise timely and successful operation for the removal of cancer from the lower bowel. Urinary tract complications, their type and severity, are often the factor upon which depends the return of the patient to a normal, comfortable life following abdominoperineal resection.

INCIDENCE

A review of statistical analyses presented by various authors with regard to urologic complications reveals a striking dissimilarity of their incidence among various operators. Hill, Barnes and Courville[7] in 1937 made a report on questionnaires sent to surgeons throughout the country. Four replies reported no complications, while seven claimed 100 per cent of their patients had some form of vesical dysfunction following rectosigmoid surgery. Thirty-two reported similar complications in 50 per cent and over, and 20 found that they occurred in two-thirds or more of their patients. Ewert[5] in 1941, reported 30 per cent urologic complications in 750 unselected patients; in which group the operability rate of rectal carcinoma was 85 per cent. Marshall[10] in 1946, reported 9.6 per cent vesical dysfunction from a series of 600 large bowel operations, most of which were for carcinoma.

Urologic difficulties following abdominoperineal resection are the result of urinary tract infection, urinary retention, local extension of the cancerous process to the urinary tract, or surgical injury suffered during the operative procedure.

Infection is undoubtedly the most frequent type of complication. It varies from a mild cystitis to the more severe forms of bladder infection associated with unilateral or bilateral pyelonephritis, a serious event in the elderly patient. It seems likely that some degree of infection in the urinary tract is a universal occurrence following this operation. The necessity of vesical drainage for seven to ten days of the postoperative period makes this inevitable. Meticulous care and proper management can minimize but not prevent infection. About one-third of the cases collected by Ewert[5] had only urinary infections as their complication.

Urinary retention, persisting beyond the immediate postoperative period, is probably the most important of the urologic problems secondary to this operation. This again is a complication which occurs to some degree in all patients, recognized by the necessity of routine catheterization. Prolonged retention requiring special care occurs in about 10 per cent of the cases. Manifested by symptoms ranging from complete retention to chronic retention with

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frequency, urgency, difficulty in voiding, and incontinence, it is found more commonly in the male than the female. Ewert and Hoffman[6] reported retention in 14 per cent of all males and 4.1 per cent of females. Kirckham and Bruce[18] found urinary dysfunction in 60.7 per cent of male patients they studied and 46.6 per cent of the female patients. Retention in the female is not mentioned by Marshall,[10] or Seaman and Binnig.[14]

Contiguous extension to and invasion of the prostate, seminal vesicles, bladder and ureters may be seen in any but the very earliest of cancers of the rectosigmoid. No accurate estimation of the incidence of such spread can be arrived at from the literature. Dixon and Benson[2] reported 64 cases in which they found bladder invasion by carcinoma of the sigmoid and rectosigmoid. In postmortem examinations on 132 cases Kirckham and Bruce[8] found ureteral involvement and obstruction in 47.7 per cent; involvement of the prostate was found in 31.5 per cent in 98 male patients. In studying the clinical records of 440 cases, they found 96 in which adherence of the rectum to the prostate could be demonstrated on digital examination. Emmett and Cristol[3] and Engel[4] have described cases with secondary invasion of the vesical neck from carcinoma of the bowel. Recurrence of tumor in the prostate is not uncommon and has been described by Engel[4] and Oppenheimer.[13] Oppenheimer has pointed out that the more advanced the primary rectal lesion the greater the likelihood that the patient will have secondary invasion of the bladder and prostate following extirpation.

Surgical injuries to the urinary tract during the course of abdominoperineal resection may create extremely difficult problems. The close anatomical relation of the urinary tract to the lower bowel creates a definite hazard to the operator. In the hands of experienced operators these accidents are rare; their incidence in the hands of the average surgeon cannot be estimated.

ETIOLOGY

The fundamental causes of infection, tumor invasion, or surgical injury need no discussion. The causes of postoperative retention, however, are not so clear. Temporary urinary retention may be seen after any operative procedure but more commonly following lower abdominal and pelvic operations. However, inability to void effectually following abdominoperineal section is so characteristic as to become an accepted part of the postoperative picture. The universal use of indwelling catheter as a routine postoperative measure is evidence of this. Fortunately, the average patient will be able to void by the seventh to the tenth day and at this time the catheter may be removed. Vesical dysfunction lasting longer than ten days requires special care and management, and may be a very difficult and disabling complication.

The cause of urinary retention following abdominoperineal resection is not clearly known. It may manifest itself as complete inability to void, chronic retention with marked frequency and bladder infection, or as a chronic retention with dribbling and overflow incontinence. Certain inherent etiologic factors must be kept in mind. Any pre-existing vesical obstruction, no matter how slight, will be exacerbated following this operation. In the male patient in the

age group commonly subjected to resection of the rectosigmoid, prostatic enlargement is common. In many instances this is well compensated for and asymptomatic during the period prior to operation. In addition to prostatic obstruction, latent urethral strictures, and as Ewert[5] suggests, even the resistance offered by the male urethra will be factors which may precipitate marked retention in the presence of the detrusor dysfunction which is so characteristic after this procedure.

Urinary retention in the absence of demonstrable obstruction, or in the presence of minimal obstruction, as is commonly seen after abdominoperineal resection, has not been adequately explained. The physiology of the bladder as it applies to this problem should be briefly considered. Normal filling and adequate emptying of the bladder depends primarily upon proper function of the detrusor muscle. The detrusor muscle normally expands and contracts uniformly. As the bladder fills it accommodates itself gradually to the increased volume, so that up to the point where a desire to urinate is noted, the intravesical pressure remains small and about constant, ranging from 4 to 6 mm. of Hg. This ability of the detrusor to accommodate is apparently independent of central nervous control. As the bladder empties itself, the detrusor contracts simultaneously from all sides, so that the entire bladder wall except for the small area of the trigone is shortening and compressing inward in a uniform manner, increasing the intracystic pressure to about 15 mm. of Hg. and, when empty, assuming a shape like that of a flattened tetrahedron. The contraction of the bladder is associated with the coincidental relaxation of the autonomic internal and the voluntary external sphincter, a relationship which must be closely and carefully co-ordinated. Anatomical prerequisites of normal vesical function are an adequate nerve supply, absence of abnormal obstruction at the outlet, and a tonic and freely movable bladder wall.

Several factors are present in the operation of abdominoperineal resection which could conceivably affect this delicate mechanism. One of the earliest theories is that postabdominoperineal vesical dysfunction is the result of injury to the nerve supply of the bladder. McCrae[11] postulates that urinary retention following abdominoperineal proctosigmoidectomy is of neurogenic origin, the result of trauma to, or removal of the inferior hypogastric or pelvic plexus. Using cystometric studies to demonstrate his point, he believes that the sympathetic nerve supply to the bladder is maintained, and that there occurs a surgical parasympathetic denervation resulting in the loss of the important parasympathetic impulses which are known to cause the detrusor to contract. He believes the rapid improvement seen in the majority of patients is due to regeneration of the nerve supply.

A careful evaluation of these patients reveals several points which preclude the neurogenic factor, certainly as the etiology of the usual case of postabdominoperineal retention. Coller and Eastman[1] and Marshall and his co-workers,[10] have each reported series of cases studied by pre- and postoperative cystometric tracings and have concluded that there was no evidence of loss of nerve function in these bladders. Langworthy and his co-workers,[9] have shown that even after a complete unilateral denervation of the bladder, the organ is

still able to empty itself quite normally. Complete denervation of the bladder could be accomplished only after extensive and bilateral dissection in the extraperitoneal tissues of the pelvis, a technic not pursued in a routine abdominoperineal resection.

As will be noted in the consideration of the management and treatment of this problem, transurethral resection is frequently helpful. After a proper transurethral resection many of these men will return to normal, and in these patients there will be no residual evidence of a neurogenic bladder. It is true that resection of the internal sphincter will help many neurogenic bladders, but it cannot change the neurogenic status of the organ.

Those who advocate the neurogenic theory further point out the anatomical relation of the pelvic plexuses to the area dissected through in the course of freeing the rectosigmoid. The argument that pelvic dissection is a significant factor cannot be denied, for patients with only palliative colostomies do not develop this bladder dysfunction. However, a further evaluation of the relation of the pelvic dissection to nerve destruction can be made by comparing cases which were treated only by perineal dissection, or the much discussed "pull through" operation with those who had the classic Miles resection. Marshall,[10] in a careful analysis of 600 cases from New York Hospital, found that in 99 cases which had only the perineal resection without dissection from above, there was an incidence of bladder dysfunction in 29.29 per cent, and in 265 who were subjected to the combined abdominoperineal dissection, the incidence of dysfunction was 27.16 per cent. Certainly from an anatomical point of view, dissection of the pelvis from above would be more likely to injure the pelvic autonomic plexuses than would perineal section alone.

It is to be noted that similar dissections done in a series of individuals results in bladder difficulty in only a third or less, and, along the same line, it occurs much less commonly in women than men.

A second general etiologic theory is supported by Emmett,[3] Coller,[1] Marshall and his group,[10] Ewert,[5] Seaman,[14] and others, who concur in their distrust of the neurogenic theory. They believe that the most important factor is change occurring in the bladder as a result of the loss of its perineal supports subsequent to the removal of the rectum and sigmoid. There is, however, much difference in opinion as to just exactly how the anatomy of the bladder is altered by this loss of posterior support. Ewert[5] described the development of a male cystocele, others believe that there is an acute angulation and kinking of the bladder neck, Marshall *et al.*[10] believe it is due to an actual descent of the bladder, with distortion of the sphincter supports. Emmett[3] believes that sufficient generalized lack of support will result in an imbalance between detrusor and the vesical neck, the latter becoming obstructive to the unsupported and distorted bladder muscle.

None of these explanations can be applied to every case. Cysto-urethrographic findings are not consistent, cystometric studies certainly have been of little value, the cystoscopic picture varies as to the position and configuration of the bladder floor, and the response to transurethral resection is not con-

sistent, all of which suggests that there is still another common factor, variable though it may be, which enters into these bladder pictures. The fact that many patients with severe bladder dysfunction in the early postoperative period gradually improve, and even return to normal under intelligent, conservative, and expectant urologic treatment, is not explained. In Marshall's series he found that whereas in his 600 cases 19.66 per cent of them had what he termed severe urinary difficulties, after a three-month period of conservative management, only 2.83 per cent had to be subjected to corrective surgery.[10]

On the basis of careful cystoscopic examination of the bladder following an abdominoperineal resection, we have noted that the most common observation is the fixation of the bladder wall manifested by a lack of mobility as it is passively emptied. This has led to a postulation that a pericystitis, traumatic in origin, is the cause of the inability of the detrusor to function normally.

We were recently required to do a cystotomy on a male patient seven days following an abdominoperineal proctosigmoidectomy. The bladder was found to be distended and tense. The prevesical tissue was edematous, which state was thought to be due to posterior urethral trauma from ineffectual catheterization. However, the edema was found to extend down both lateral walls and the perivesical tissue between the peritoneum and fundus of the bladder was also edematous. The bladder wall was firm and of normal thickness. After opening the bladder it was necessary only to separate the wound edges to inspect the entire vesical cavity. The bladder wall was fixed and rigid due to extravesical inflammatory changes, so that its entire cavity could be inspected without retraction, as one might open and view the inside of a hollow rubber ball.

The patient had had no preoperative urinary symptoms or difficulty. He had had no unusual infection as the result of the rectal surgery, and had a minimal febrile reaction. As far as the operation was concerned the convalescence was uneventful except for urinary retention. There was no evidence of urinary extravasation which might have caused the pericystitis. It was an aseptic inflammatory reaction which was considered the result of trauma accompanying the operation.

The rotund, fixed bladder wall surrounded by edematous areolar and adipose tissue represented a striking picture, the cause for which could not be ascribed to intraurethral or intracystic manipulation or infection. Extravesical infection was not evident as an extension from the perineal wound or extravasation from the urethra. Trauma from manipulation or retraction at the time of the abdominoperineal operation appeared to be the only cause. Subsequent cystoscopy has revealed that this patient's bladder wall has regained its normal mobility.

Cystotomy in these patients is such a rare procedure that it makes visual observation of this pathologic condition in a series of patients impractical for proof of the hypothesis. However, cystoscopic and panendoscopic observation of the bladder in the postoperative patient has enabled us to demonstrate the inflexibility of the vesical wall. Fixation of the bladder base and posterior wall was the characteristic finding; however, in some, immobility of the lateral

vesical walls was also noted. A male patient who had been unable to void on removal of his catheter on his seventh and ninth postoperative days was examined on the tenth day. It was noted that the anterior wall from the vesical neck to the air bubble moved freely on filling and emptying the bladder, but that the posterior and lateral walls seemed rigid and fixed. Suprapubic pressure was then applied to forcibly express all the fluid from the bladder. The bladder did not collapse, and, with the stopcocks of the instrument remaining open to allow for free drainage of the bladder, it was possible to visualize the posterior wall of the fundus as well as most of the lateral walls. There were no marked mucosal or inflammatory changes. The bladder wall was fixed from an extravesical cause, not from an intramural or intravesical pathologic change.

Two patients known to have moderate degrees of prostatic hyperplasia were examined on their fourteenth postoperative day. In each of these the immobility was limited to the bladder base and posterior wall, the lateral walls being freely movable on distension and emptying. Subsequent transurethral resection was necessary to relieve retention in these cases, at which time the posterior wall was found to be mobile.

A somewhat similar cystoscopic observation has been recorded by Seaman and Binnig,[14] but not attributed to the same etiologic factor. Coller and Eastman,[1] after concluding that abdominoperineal resection destroys neither the autonomic nor somatic nerve supply to the bladder, have suggested that local trauma may be the cause of retention in cases they have observed.

The dissection of the vesical space with associated trauma due to traction, pulling, etc., no doubt results in marked perivesical and vesical edema, hematoma formation, tissue injury with secondary fibrosis, injury to blood supply, and injury to the bladder wall itself. It is not uncommon to see evidence of minor bladder injuries on cystoscopic examination following much less traumatic pelvic or lower abdominal procedures. The fixation of the wall, whether it be acutely retroflexed or not, results in altered functional ability of the detrusor to contract as it did in its normal state. If this fixation is associated with gross anatomical displacement of the bladder neck, a male cystocele, or other abnormality, these naturally will exacerbate the pathologic physiology.

This hypothesis can also explain many of the points so strongly emphasized by others. The "dome shaped" bladder observed by Hill, Barnes and Courville[7] on cystographic studies done on the sixth postoperative day, with a more normal bladder on the twelfth postoperative day, represents the picture we visualized at the operating table, and the regression observed on subsequent examination. Inflammatory paralysis or fixation of the bladder wall can certainly result in a neurogenic type picture, and even a neurogenic type cystometric curve. The gradual improvement in these patients is the result of normal healing processes, restoration of blood supply, and the restoration of texture of the perivesical tissues.

The low incidence of this complication among females is owing to the protection afforded by the anatomically interposed female genital organs. We have observed prolonged dysfunction in two female patients, both of whom

had previously had total hysterectomies. The incidence of previous hysterectomy has not been noted by authors reporting female patients in their series.

TREATMENT

The treatment of vesical dysfunction is the most common urologic problem following abdominoperineal resection. Traumatic aseptic pericystitis is transient and self limiting. It accounts for the temporary difficulty in voiding for the first seven to ten postoperative days. This pathologic change, *per se,* causes no concern, but requires catheterization, which in turn inevitably invites infection. This type of vesical dysfunction being the most frequent complication limits the majority of care to the treatment of infection.

Constant catheterization with tidal drainage has proved to be the most satisfactory initial treatment. The catheter is removed on the morning of the seventh postoperative day. Twelve hours later the patient is catheterized for residual urine. If this is over 100 cc. the catheter is fixed in the bladder and the procedure repeated the following day. If the patient cannot void, or if the residual urine remains above 100 cc. the patient is cystoscoped for evidence of vesical outlet obstruction.

It is generally accepted, and it has been our observation, that prolonged retention of urine is the result of vesical outlet obstruction. The great majority are promptly relieved by transurethral resection of the prostate gland, or vesical outlet. Failure to re-establish normal micturition is usually due to incomplete removal of obstructive tissue. The prolonged recovery of detrusor tone in a few cases requires a long period of catheter drainage. Marshall[10] has advocated vesical suspension for retention which exists over a period of three months, based on his theory of vesical neck angulation.

Ureteral injury, the result of ureteral section, or denudation, which is manifested by perineal drainage is, at the best, a very uncomfortable complication, and may become serious if infection and the necessary correction by nephrectomy ensue. If ureteral injury is recognized at the time of the rectal resection, ureterovesical anastomosis can be performed, provided the length of the ureter will permit. Ureteral ligation with the hope of producing an acute renal atrophy can be performed, presupposing a functioning contralateral kidney. Failure to recognize the injury, or to correct it at the time of rectosigmoid surgery, results in a persistent ureteroperineal fistula which can only be corrected by ureterodermal transplant, uretero-enterostomy, or nephrectomy.

Invasion of the lower urinary tract by carcinoma from the rectum, especially when it arises in the anterior wall, occurs with sufficient frequency to warrant consideration. Late invasion of the bladder and prostate occurs in 31 per cent of patients.

The attachment of the involved rectal wall to the prostate or bladder may be due to an inflammatory change or malignant extension, the cause of attachment in any case being impossible to identify at the time of rectal surgery. Proposal to "shave off" a portion of the prostate, bladder wall, or even urethra is frequently heard. This procedure has two faults, first, the possibility of

leaving residual malignant tissue which can defeat an otherwise successful operation, and secondly, the disturbance of the local circulation, producing necrosis, which results in incontinence or a perineal fistula. We have seen one patient with a persistent perineal fistula which has defied repair, and has made the patient's life miserable for an eight-year period following the successful removal of a rectal carcinoma. This man's prostate was "shaved off" too closely and the entire posterior urethra and a portion of the membranous urethra sloughed away.

Total removal of the prostate with its capsule and the seminal vesicles is indicated when there is any suspicion of the attachment or contiguous extension of the rectal lesion to these organs or their enveloping fascii. Radical removal is also indicated when there is suspicion of involvement of the bladder. Localized invasion may be treated by segmental resection of the bladder and more extensive spread by prostato-seminovesical cystectomy. The latter procedure obviously necessitates the transplantation of the ureters to the skin or to the bowel proximal to the colostomy.

The feasibility of block removal of the prostate gland and posterior urethra can be demonstrated by the following case report:

C. S., a male patient, age 61, was admitted to Hahnemann Hospital November 25, 1947, complaining of altered bowel habits for a 4-month period, mainly evident as a diarrhea. He had lost 43 pounds in weight. Symptoms referrable to the urinary tract were difficulty to start stream, with nocturia 2 to 3 times, and some dribbling. Because of the latter symptoms we were asked to see the patient. Rectal examination revealed a large growth in the bowel which completely obscured the prostate, so that nothing could be determined as to its size or the attachment of the rectal wall to the prostatic capsule.

After careful bowel preparation and general supportive therapy, an abdominoperineal resection and colostomy was performed December 11, 1947. At the time of the perineal resection the bowel was readily dissected from the bladder and urethra, but appeared to be intimately attached to the prostatic capsule. We were consulted at this time and felt it would be advisable to remove the prostate gland and posterior urethra with the rectum. We joined the operating team and performed a block resection of the urethra. It was necessary to remove a large portion of the trigone with the posterior urethra and prostate. An end-to-end anastomosis of the urethra and bladder was consumated about a Foley catheter without difficulty, the bladder being closed transversely.

There was no perineal leakage of urine during the postoperative period. At the end of 14 days the urethral catheter was removed and the patient voided well without perineal leakage. Continence was not complete, as evidenced by slight dribbling when he was on his feet, but was not sufficient to necessitate a urinal or penile clamp.

Pathologic studies of the rectum revealed an adenocarcinoma. Sections of tissue from the region of the prostate and the attached rectum revealed "stromal infiltration of the capsule." The gland itself was not involved by the malignant process.

The patient was discharged January 6, 1948, but was readmitted March 17, 1948, with symptoms of bowel obstruction. A laparotomy performed March 22, 1948, revealed extensive visceral and mesenteric lymph metastasis from the primary rectal growth. Examination of the perineum revealed no evidence of local recurrence of the growth. The patient died April 29, 1948 from extensive carcinomatosis.

No conclusions can be drawn from this case report concerning the possibility of total prostatectomy to increase longevity, but the feasibility and ease

of performing total prostatectomy at the time of perineal dissection when there is suspicion of prostatic involvement, is clearly demonstrated.

The prostate gland and its capsule can be removed with ease. Primary wound healing can be obtained if the urethral and vesical stumps are not devascularized during rectal resection. Firm and accurate closure followed by careful and meticulous toilet of the perineal sinus will minimize the possibility of wound infection to insure successful closure of the anastomosis.

SUMMARY

Urologic complications following excision of rectal carcinoma results in a high incidence of prolonged postoperative invalidism. The reported incidence of infection, vesical retention, surgical injury and tumor invasion is noted.

A traumatic aseptic pericystitis is suggested as the etiology of bladder retention seen following abdominoperineal resection.

The management of persistent vesical retention and surgical injury is discussed.

Total prostatectomy, segmental resections of the bladder, or total cystectomy is indicated where the lesion is adherent to or has invaded these organs.

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THE SURGICAL TREATMENT OF DIVERTICULITIS OF THE COLON*

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DIVERTICULITIS OF THE COLON has been traditionally regarded as a condition to be treated conservatively. Surgical textbooks and surgical teaching have long advised against a radical approach to this condition, operative intervention being reserved only for those patients who develop abscess, peritonitis, obstruction, or fistula. In the event of these complications, the common practice has been the employment of the most conservative surgical measures in the hope that diverticulitis will not recur.[1-15] Simple drainage of abscesses with or without colostomy has been customary. In case of obstruction or fistula (cutaneous or vesicocolic) colostomy has been advocated, the fecal shunt being maintained for three to 12 months in order to place the involved bowel at rest. After such prolonged periods of decompression it has been common practice to close the fistula and re-establish bowel continuity without removal of the diseased segment.

This conservative attitude was advocated in the era prior to the introduction of chemotherapy and the antibiotics and resulted from the high mortality rate reported when resection was undertaken. Since 1941, a few reports[16-20] have decried the poor end-results from conservative surgery in complicated diverticulitis and have suggested performance of earlier curative resection. However, conservatism has persisted despite the fact that measures short of resection have yielded prolonged morbidity and distressingly high recurrence rates. It has continued in many clinics without regard to the marked reduction in mortality following resection, reported in the recent literature.[17, 19] Furthermore, the great strides of recent years in the reduction of morbidity and mortality following surgical treatment for carcinoma of the colon have been largely disregarded in the re-evaluation of surgical therapy in diverticulitis.

However, many patients with diverticulitis, both in the acute phase of the disease and in the more chronically complicated stages of obstruction or fistula, require early resection because of the difficulty in ruling out carcinoma. This diagnostic problem is well illustrated by two case reports from the Massachusetts General Hospital.[21] One patient, observed for a long period under the diagnosis of diverticulitis, proved eventually to have hopeless carcinoma of the sigmoid. A second patient with both clinical and roentgen evidence of carcinoma underwent early resection for a lesion which proved to be diverticulitis.

During a recent ten months' period three patients came under my

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observation in whom the diagnosis of carcinoma of the sigmoid could not be ruled out prior to pathologic examination. In two of these patients, from the clinical findings, the diagnosis of diverticulitis seemed most likely. One presented the typical inflammatory picture so common in this disease, while the other had developed a spontaneous vesicosigmoidal fistula. However, roentgen evidence of cancer was found in both (Figs. 1 and 2). The third patient was admitted with large bowel obstruction, requiring colostomy decompression. Abdominal exploration at that time revealed a large rectosigmoidal mass, appearing grossly malignant. In two of these cases diverticula were not

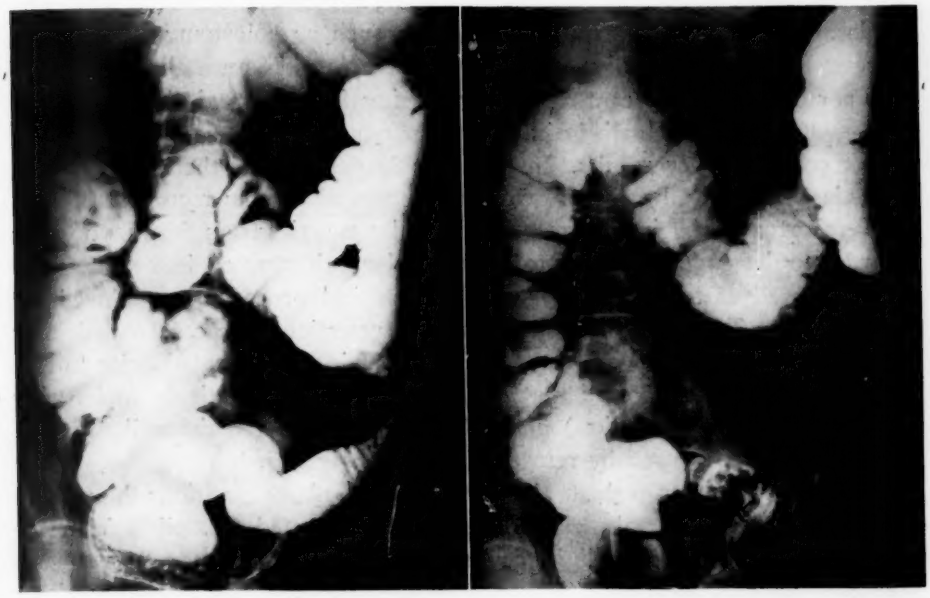

FIG. 1 FIG. 2

FIG. 1.—Barium enema showing persistent defect in sigmoid colon. No diverticula are seen. The clinical picture suggested diverticulitis. Palpable mass in left lower quadrant. Roentgen ray consultant could not rule out cancer.

FIG. 2.—Barium enema showing annular defect of sigmoid colon. Numerous diverticula are seen. Roentgen ray consultant could not rule out cancer, although diverticulitis was suspected. The clinical picture is that of spontaneous vesicosigmoidal fistula of four weeks' duration

demonstrated by roentgen ray. Resection of the involved segment was performed in each instance, the first two in one stage and the third after preliminary colostomy. At operation all of the lesions appeared grossly malignant, the true condition not being apparent until the bowel had been examined by the pathologist. Carcinoma was found in none.

This experience pointedly raised a number of questions regarding the traditional therapy in this disease. If early resection can be done successfully in cases in which the diagnosis of carcinoma is falsely made, should it not be considered as well in the majority of complicated diverticulitis cases? Is the mortality from resection prohibitive? Is the chronic morbidity incident to

prolonged colostomy drainage necessary? What are the late results following resection as compared to less radical measures?

The answers to these questions are not immediately apparent. Since the disease is comparatively rare it is difficult for any individual to accumulate enough personal experience to permit divergence from the accepted pathways of treatment. However, two large series have been reported in recent years which throw light on some of these problms. Smithwick,[17] in 1942, reviewed a 15 years' experience from the Massachusetts General Hospital. He reported 64 cases of surgically treated diverticulitis, in 33 of which resection had been performed with two deaths, a mortality of 6.1 per cent. He pointed out that the late results from less radical measures, such as colostomy, drainage of abscess, or closure of fistulas, were poor. Those classed as unwell amounted to 47.5 per cent, 78.9 per cent of these requiring further surgical intervention. Those who subsequently died of their disease amounted to 12.5 per cent. Thus, 60 per cent had poor results. In contrast, 84 per cent of the resected cases were classified as well and there was no late mortality from recurrent disease.

Pemberton *et al.*[19] in 1947 compared two large series from the Mayo Clinic in order to determine the effect of modern chemotherapy on immediate mortality, as well as to appraise the various surgical procedures employed for diverticulitis. The immediate mortality for resection in cases treated after 1940 was 2.7 per cent in contrast to 16 per cent in those treated prior to that date. They further reported that only one-third of the patients undergoing colostomy (without resection) and subsequent closure remain well. Preliminary colostomy followed by resection was strongly urged.

In order to further evaluate the answers to the above questions the present review has been undertaken. The data here presented, compiled from the records of The Portland Clinic, cover a 20-year period (1929 to 1949) in which 37 patients with diverticulitis were treated surgically. Many patients with acute diverticulitis were treated conservatively and did not require surgery. These cases are not included in this review. All cases of carcinoma of the colon have been excluded. Although the work of five surgeons is represented, the majority of the patients were operated on by the late Dr. Thomas M. Joyce. It is interesting to note that Doctor Joyce treated this disease by early attack on the diseased segment of bowel, commonly by primary resection. He did not practice prolonged colostomy drainage. The resultant decrease in morbidity has been an illuminating feature of the present study. Twenty-six of the 27 patients whom he personally treated underwent resection, the remaining patient being referred to him for colostomy closure with no demonstrable residual diverticulitis. It has been gratifying to find that the results obtained completely justified his practice.

INCIDENCE AND DISTRIBUTION

Diverticulosis of the colon occurs in approximately 5 per cent of people over 40 years of age.[9] It is also estimated that approximately 10 per cent of these develop diverticulitis,[9] and further, that of those with diverticulitis,

about 10 per cent will require surgical intervention.[17] This means that approximately 1 in 2,000 people over 40 years of age come to operation for this disease. It is obvious that few surgeons will acquire an extensive experience in its treatment.

Diverticulosis may occur throughout the colon (14.4 per cent), but is most commonly seen in the sigmoid and rectosigmoid (72.0 per cent).[22] The cecum is involved in 4.8 per cent, the rectum in 2.4 per cent.[22] The incidence of inflammation in diverticula above the level of the sigmoid is rare. Smithwick[17] mentioned only two cases treated at the Massachusetts General Hospital in a 15-year period, the lesions occurring in the cecum and ascending colon, respectively. In the 20-year period covered by this report two cases involving the cecum and one involving the ascending colon were encountered. The latter case is of particular interest since acute perforation of a diverticulum of the ascending colon requiring resection occurred two years after resection of the sigmoid for diverticulitis.

TABLE I.—*Age by Decades—35 Cases of Sigmoid Diverticulitis Undergoing Surgery.*

Decades	Cases	Per Cent of Cases
40–49	7	20
50–59	13	37.2
60–69	9	25.7
70–79	6	17.1
Total	35	100

CLINICAL PICTURE

In a collective review, Smithwick[17] found over 87 per cent of the cases occurring in the fifth, sixth, and seventh decades of life. Thirty-five cases of sigmoid diverticulitis occurred in the series under consideration. The average age was 58.6 years at the time of operation. The youngest was 40 years of age, the oldest 78. Table I shows the incidence by decades. Two-thirds of the patients were over the age of 55. The three patients with involvement of the right side of the colon were 29, 35, and 54 years of age, respectively.

Although the sex incidence in collected series shows that the disease is more common in men than in women, the present series includes 19 men and 18 women.

The symptoms and signs which the patients presented are summarized in Table II. The heading of inflammation includes such findings as fever, chills, tenderness, rigidity, and leukocytosis. Twenty-three of the cases (67.6 per cent) fell into this category. Hemorrhage occurred in four patients, and was the presenting symptom in three. Diarrhea was noted in seven. An abdominal or pelvic mass was palpable in 50 per cent of the patients. Fistulas were present in only three, a lower incidence than commonly reported. Complete or partial intestinal obstruction was encountered in 11 patients, in seven of whom colostomy was necessary. In one case, small bowel obstruction developed due to adhesion to a perforated diverticulitis. Release of adhesions gave

relief, but recurring bouts of diverticulitis required resection eight months later.

The majority of cases of diverticulitis are diagnosed without great difficulty, and respond well to nonoperative treatment. The complications of the disease which require surgical attention include free perforation into the peritoneal cavity, abscess, fistula, and obstruction. Blood in the stools or

TABLE II.—*Symptoms and Signs of Diverticulitis of Sigmoid in 34 Cases in Which Surgery Was Performed.*

Symptoms or Signs		Cases	Per Cent of 34*
Inflammation		23	67.6
Intestinal obstruction, complete or partial		11	32.4
Diarrhea		7	20.6
Hemorrhage		4	11.8
Mass		17	50
Abdominal	6		
Pelvic	9		
Both	2		
Fistula		3	8.8
Sigmoidal cutaneous	1		
Sigmoido vesical	2		

* Right colon cases eliminated. One case eliminated with only closure colostomy. Many cases showed more than one of above findings.

severe hemorrhage occurs in about 15 per cent[17] of the cases (11.8 per cent of this series) and requires close differentiation to rule out carcinoma. Jones[23] advocated operation in all cases showing hemorrhage for fear of missing carcinoma. As has been pointed out, the diagnosis of carcinoma cannot be eliminated in many cases either clinically or by roentgen ray. Other patients are operated on under the mistaken diagnosis of tumors arising from the female pelvic organs.[24]

TABLE III.—*Results of Preoperative Barium Enema Examination in 24 Cases of Complicated Sigmoid Diverticulitis.*

Xray Findings		Cases
Diverticulitis		14
With perforation	4	
Carcinoma		2
Possible carcinoma		7
Obstruction		6
Narrowing with pericolic mass		1
Spasm of sigmoid only		3
Negative		1

Schatzki[25] pointed out that barium enema permits accurate diagnosis in most cases of diverticulitis, but that difficulty in differentiating carcinoma is not uncommon and occasionally impossible. Preoperative barium enema was carried out in 24 cases of sigmoid diverticulitis. Table III shows the findings reported. Carcinoma was definitely diagnosed in two and mentioned as a possibility in seven others. Sigmoid obstruction was encountered in six cases and narrowing of the sigmoid with pericolic mass in one other. Spasm of the sigmoid was the important notation in three. In one case the barium enema

was reported as negative. Diverticula and evidence of diverticulitis were noted in 14 cases, four of which showed perforation with extravasation of barium outside the lumen of the bowel.

Sigmoidoscopic examination was of little diagnostic aid. It was performed in 12 cases, with negative findings in six. Obstruction was demonstrated in five cases. One of these showed an ulcerated area at the site of obstruction, biopsy of which was reported benign on two occasions. In another case showing obstruction, a benign polyp was found distal to the obstruction. Early ulcerative colitis was mistakenly diagnosed in one case.

Table IV lists the preoperative diagnoses taken from the operative records of the cases of sigmoid diverticulitis in the present series. Only seven cases

TABLE IV.—*Preoperative Diagnosis in 34* Cases Recorded at Time of Surgery and in 9 Cases in Which Resection Was Performed at Subsequent Stage.*

Preoperative Diagnosis	Primary Operation		Subsequent Surgery Except Colostomy Closure	
	Cases	Per Cent	Cases	Per Cent
Diverticulitis	7	20.6	3	33.3
Carcinoma of colon	5	14.7	2	22.2
Diverticulitis? Carcinoma?	10	29.4	4	44.4
Pelvic tumor	7	20.6		
Abdominal or pelvic abscess	5	14.7		
Total	34	100	9	100

* One case, entering for closure of colostomy only, has been eliminated.

were correctly diagnosed before the primary operation. Some form of pelvic tumor was the preoperative diagnosis in seven cases. Carcinoma was the unqualified diagnosis in five cases, and could not be ruled out in an additional ten. Thus, in 44.1 per cent, primary operation was undertaken early because of the mistaken possibility of cancer of the bowel. It is of interest to note that in nine cases, at the time of second stage operations other than colostomy closure, the preoperative diagnosis included the possibility of carcinoma in six. This emphasizes the difficulty in gross pathologic differentiation at the operating table.

OPERATIVE TREATMENT

The operative procedures carried out on the 37 patients in this series are of interest. As mentioned above, one case of sigmoid diverticulitis returned two years after resection of the sigmoid with an acute perforation of a diverticulum of the ascending colon. This patient has been included twice in this series, bringing the total cases treated to 38.

Of the three patients with involvement of the right colon, two suffered acute perforations and, as emergencies, underwent one stage right colectomy with ileotransversostomy. They were discharged ten and 19 days following resection and have remained well 13 and 17 months postoperatively. One complained of occasional mild diarrhea following operation.

The third patient was admitted with a retroperitoneal abscess posterior

to the cecum, having previously been operated on elsewhere because of a right subdiaphragmatic abscess. Following drainage of the retrocecal abscess a fecal fistula developed. Barium enema revealed diverticula of the cecum and transverse colon with a fistula from the cecum. Right colectomy was performed two months later. A residual sinus persisted which required treatment for 18 months before it finally closed. The patient was in good health eight years following resection.

In the remaining 35 cases the disease involved the sigmoid. In six of these, operative treatment other than resection was carried out. Table V lists the type of operation and the late results in these conservatively treated patients. In three cases, classified as not well, resection was later necessary, one because of a persistent fecal fistula and two because of recurrent bouts of severe diverticulitis. Three patients recovered without further operation. In one, drainage of a large perisigmoidal abscess was performed. A resulting sinus closed and reopened, due to recurring abscess, twice within six months, following which it healed. The last report revealed the patient to be well seven years from the date of operation. In another patient a large pelvic abscess was drained and colostomy performed because of obstruction at the rectosigmoid. The colostomy was closed three months later, the patient remaining well without recurrence 19 years thereafter. The third patient entered for closure of a transverse colostomy performed elsewhere. Roentgen evidence of diverticulitis had entirely disappeared. Follow-up reports revealed the patient to be in good health without recurrent disease five and a half years after closure of the colostomy. This experience corroborates the reports of others[17, 19] that surgical intervention short of resection yields a high recurrence rate.

TABLE V.—*Operations Other Than Resections for Diverticulitis of Sigmoid Colon. Postoperative Complications and Late Results.*

Operations	Cases	Deaths	Postoperative Complications*		Late Results	
			Cases	Number	Living & Well	Not Well
Drainage of abscess	3	0	1	1	1	2
Drainage of abscess with colostomy—later closure	1	0	1	1	1	0
Release small bowel obstruction due to adhesions	1	0	0	0	0	1
Closure colostomy only	1	0	0	0	1	0
Total	6	0	2	2	3	3

* Two cases of incisional hernia.

Table VI delineates the operative treatment of 31 patients on whom various methods of resection were carried out. One patient on whom two resections were done has been omitted from this chart because her course was too complicated to permit tabulation. The details of her treatment, which resulted in complete failure, will be briefly outlined later. The patients listed in Table V as not well, later requiring resection, are included in Table VI.

Twenty-one patients were treated by primary resection and end-to-end anastomosis, ten with complementary cecostomy and ten without cecostomy. One of the latter was complicated by the development of a fecal fistula. Transverse colostomy was carried out three weeks later. The fistula promptly healed, permitting colostomy closure three months thereafter. One patient, with involvement of the rectosigmoid, was explored as an emergency under a mistaken diagnosis, a pelvic abscess found, and resection and end-to-end anastomosis with complimentary transverse colostomy performed. The colostomy was closed two months later.

TABLE VI.—*Resections—All Methods—For Diverticulitis Left Colon—Including Postoperative Complications.*
Late Results (Followed 1 to 16 Years)
Early Results (Followed Less than 12 Months Postoperatively)

Type of Operation	Cases	Deaths	Postoperative Complications		Late Results		Early Results	
			Cases	Total Number	Living & Well*	Not Well	Living & Well†	Not Well
PRIMARY RESECTION	21	0	5	9	15	0	5	1
End to End Anastomosis								
With complementary cecostomy 10								
With complementary colostomy and later closure colostomy 2								
Without complementary cecostomy or colostomy 9								
MIKULICZ (OBSTRUCTIVE) RESECTION	3	0	1	1	3	0	0	0
Second stage closure of resulting colostomy								
TWO STAGE LEFT COLECTOMY	1	0	1	1	0	0	1	0
Resection descending and sigmoid colon—proximal loop exteriorized and closure distal stump								
Mobilization transverse colostomy and anastomosis to rectosigmoid—complementary cecostomy								
THREE STAGE RESECTION	6	0	2	5	4	0	2	0
Transverse colostomy								
Resection and end to end anastomosis								
Closure colostomy								
Total	31	0	9	16	22	0	8	1

* Three subsequent deaths—unrelated cause.
† One subsequent death—unrelated cause. One death—cause and date unknown.

It is worthy of note that all cases with complementary cecostomy were treated prior to 1943. Only two of the ten cases resected without cecostomy were treated before this date, the remaining eight having been operated on since 1946. No cecostomy required closure. The value of cecostomy as an adjunct to resection is difficult to ascertain from the case records. It is doubtful that it would have been adequate protection in the patient who developed leakage at the suture line. As will be mentioned later, the short segment resected in this case was more likely the cause of this complication. That cecostomy has been discarded in recent years may be significant.

Mikulicz resections were performed in three cases, all prior to 1937. The indications for this procedure were not clear from the records. In one case,

partial obstruction was the obvious reason for this choice. Severity of the process was no greater in the other two than in many subjected to one stage resection. The location of the lesion to permit exteriorization of both ends following resection was certainly not the deciding factor, since in only five of the primary one stage resections was the rectosigmoid involved. The remainder were located high enough to permit obstructive resection had the surgeon desired.

Three-stage operations (transverse colostomy, resection and end-to-end suture, and closure of colostomy) were carried out on six patients. All of these have been done since 1944. In four cases, the indication for the preliminary colostomy was obstruction. Inadequate bowel preparation was the reason for colostomy in one case operated on as an emergency under a mistaken diagnosis. In one case barium enema revealed a large extracolic cavity, the result of perforation of a diverticulum. Preliminary colostomy seemed wise.

The duration of these six colostomies prior to resection ranged from two to nine weeks, the average being just over four weeks. In five of these cases carcinoma was suspected, requiring early definitive surgery. In the sixth, in which a definite diagnosis of diverticulitis was made, resection was performed two weeks after colostomy. This patient was treated in October, 1948. The decision to carry out early resection was made in the light of past experience at the Clinic and is in sharp contrast to accepted teaching.

The remaining case tabulated in Table VI was that of a patient who had severe diverticulitis involving the sigmoid and descending colon. Perforation of the bowel had resulted in a large retroperitoneal abscess which extended over the entire left iliac fossa and adjacent lumbar area. This cavity filled with barium on roentgen examination. Drainage of this abscess resulted in a fecal fistula which necessitated further operation. The descending colon and extrapelvic sigmoid from a point three inches above the peritoneal reflection were resected. The distal stump of sigmoid was closed and the proximal limb at the splenic flexure brought out as a colostomy. Two and a half months later, anastomosis of the transverse colon to the pelvic sigmoid was accomplished, complementary cecostomy and sphincterotomy being added at the conclusion of the procedure. The patient was in good health, aside from an incisional hernia, when last seen six months thereafter.

LATE RESULTS

The late results of the resected cases also are included in Table VI. Twenty-two patients have been followed one year or more, the longest follow-up being 16 years. Three have died of unrelated causes. All of the 22 patients have been classified as living and well as far as diverticulitis is concerned. As previously mentioned, there was one complete failure in a resected case not included in the table because of difficulty in tabulation. Thus, 95.65 per cent of 23 patients who submitted to resection were cured of their disease. Of nine patients followed less than 12 months, only one is classified as unwell.

She was last seen seven and a half months following resection, at which time a sinus persisted in the abdominal wound. Her health was otherwise good. Two of the nine are known to be dead, one of unrelated disease five months following operation, and one, cause and date unknown.

Smithwick[17] mentioned the possibility that the type of anastomosis, aseptic or open, might have some bearing on complications and late results. He found that six out of seven patients in the Massachusetts General Hospital series who had either leakage at the suture line or late symptoms, had had aseptic end-to-end anastomoses. Only one patient in the present series had an aseptic anastomosis. No early or late complications resulted, the follow-up revealing perfect health four years and four months following operation.

TABLE VII.—*Comparison of Morbidity—Various Types of Resection for Sigmoid Diverticulitis.*

Type of Operation	Cases	Average Days Hospitalization	Average Duration Disability—Weeks*	Average Duration Colostomy Weeks
1. Resection without colostomy	19	30	5.3	0
2. Obstructive type of resection	4	100	18	11†
Mikulicz 3				
Two stage left colon resection 1				
3. Resections with complementary colostomy	8	67	12	8.5
Colostomy made as first stage 6				
Colostomy at time of resection 1				
Colostomy after primary resection 1				
Total cases with colostomy (Groups 2 and 3 above)	12	78	14	9

* From first admission to final discharge from hospital—many having more than one hospital admission.

† This figure an estimate, since one colostomy was not closed but simply clamped on two occasions. Duration of colostomy in this case has been calculated to the date of second clamping, it being assumed that closure could have been accomplished on that date.

The patient not included in Table VI was first seen on November 18, 1943, with a fecal fistula which followed an exploratory operation elsewhere one year before. Her past history included two previous laparotomies, appendectomy and hysterectomy. While a patient at the Clinic she was operated on seven times, as follows: (1) December 23, 1943. Fistula communicating with sigmoid closed; bladder accidentally opened and closed; transverse colostomy. (2) January 19, 1944. Recurrent fistula closed; pelvic abscess drained. (3) March 1, 1944. Closure of vesicosigmoidal and sigmoidal-cutaneous fistulas. (4) June 19, 1944. Resection of sigmoid, end-to-end anastomosis. (5) July 13, 1944. Colostomy closure. (6) July 29, 1944. Transverse colostomy because of recurrent sigmoidovesical fistula. (7) June 25, 1945. Resection of sigmoid, end-to-end anastomosis; repair of bladder. The vesicosigmoidal fistula recurred again and was still present when the patient was last seen on January 7, 1947. Sigmoidoscopy at that time revealed a severe stricture at the site of anastomosis, 14 cm. above the mucocutaneous line. From study of the many operative reports, it is obvious that severe diverticulitis, originally

complicated by extensive postoperative adhesive peritonitis, plus a tragic surgical accident have combined to yield this apparently hopeless result.

MORBIDITY

The immediate morbidity incident to the various types of resection should be of concern to both surgeon and patient. Table VII shows the average days of hospitalization as well as the duration of disability from the first admission to final discharge from the hospital in patients who were repeatedly hospitalized. This does not imply total disability before resumption of usual activity or occupation. These data were not available. Total duration of colostomy also has been included in the table. For this tabulation the complicated case mentioned above has been eliminated.

The duration of hospitalization in cases in which resection was done without colostomy was less than one-third that of the obstructive resection cases and less than one-half that following resection in which transverse colostomy was done preliminary to or as an adjunct to resection. When the two types of resection in which colostomy closure is necessary are combined the average hospital stay is more than two and a half times that of cases not requiring colostomy. The same comparison is apparent when the duration of disability is considered. Total duration of colostomy prior to closure in the two groups in which side-tracking operations were used varied from one to three months, the average for all cases being nine weeks.

POSTOPERATIVE COMPLICATIONS

A tabulation of postoperative complications is shown in Table VIII, and the number of patients suffering complications in each group of operative procedures is listed in Tables V and VI. Wound infection was difficult to ascertain from the records. Since many of the cases were drained at the time of operation, minor wound sepsis about the site of drainage or around cecostomy tubes has not been included as a complication. The listed complications occurred about equally in the various types of procedures. Five incisional hernias occurred, one of which was complicated by acute strangulation. Three of these hernias were later repaired. Altogether 19 complications occurred in 12 patients.

Postoperative barium enema studies were obtained in 18 cases of sigmoid diverticulitis. Six of these were performed in the early postoperative period, within two months or less of resection. Obstruction was found in none, irregularity or deformity at the suture line being described in four. In one case, a small tract outside the lumen of the bowel was demonstrated two and a half weeks after resection and prior to closure of the colostomy. Thirteen patients were examined months or years after operation. No evidence of obstruction was found in any of these. Deformity at the site of colostomy closure following a Mikulicz type of resection was described in one. In seven cases, diverticula were noted. Spasm was present in four cases. Late examinations in all

patients were done merely for check-up. None were carried out because of recurrent symptoms.

PATHOLOGY

Review of the pathologic reports in the cases of sigmoid diverticulitis revealed evidence of acute or subacute inflammation in 20 cases. Suppurative changes were present in 13 cases, mesenteric abscesses being described in nine. Ulceration was noted in two cases, fistulas in three, and stricture in one. The pathologic diagnosis in nine cases was simply diverticulitis or diverticulitis with perisigmoiditis, the type of inflammation not being mentioned. Chronic diverticulitis alone was diagnosed in two cases, multiple diverticula without evidence of inflammation in one.

TABLE VIII.—*Postoperative Complications—All Cases of Sigmoid Diverticulitis—19 Complications Occurring in 12 Patients.*

Complication		Number
Pulmonary		2
Pneumonia	1	
Pneumonia with effusion	1	
Vascular		2
Femoral phlebothrombosis	1	
Pulmonary embolus	1	
Cardiac		2
Coronary thrombosis	1	
Cardiac decompensation	1	
Urinary		2
Cystitis—severe	1	
Vesicosigmoidal fistula due to bladder injury	1	
Wound complications		9
Evisceration	1	
Wound infection—severe	1	
Postoperative sinus	1	
Fecal fistula	1	
Incisional hernia	5	
Paralytic ileus	1	1
Suppurative arthritis (knee)	1	1

Smithwick[17] suggested that more extensive resections, judged by the length of the specimen, resulted in better end results. He reported that in the cases showing leakage at the suture line less extensive resections had been performed. The average length of the resected segment reported by Smithwick was 13.6 cm., with 85 per cent of the cases ranging 15 cm. and below. In only four cases was a longer segment removed. The length of the resected segments in the present series was available from the pathologic reports in 31 cases. The average length was 14.5 cm., very little greater than that reported by Smithwick. In 22 cases (71 per cent) the specimens measured 15 cm. or less, averaging 11.0 cm. However, in nine cases the resection was 18 cm. or longer, the average being 23.2 cm. In these cases the operative note signified a more extensive process, although the pathologic changes were no more severe than in the specimens of shorter length. A comparison

between the length of the resected segment in the one stage resections and in the three stage resections revealed no significant difference. The Mikulicz resections measured 12, 22, and 34 cm.

This slight difference in the present series compared with that reported by Smithwick[17] certainly cannot be construed as the reason for the improved percentage of late results. The somewhat greater length in this series is more likely the result of operation carried out in an earlier stage of the disease, before the acute process had resolved. However, it is significant that in the one failure in the group, the resected specimen measured only 5 cm. This was one of two specimens measuring 5 cm., and one of four cases in which the segment removed measured less than 10 cm. The second 5 cm. specimen was from the only case of primary resection with end-to-end anastomosis in which a fecal fistula developed postoperatively. These two cases tend to bear out Smithwick's conclusions in this regard.

DISCUSSION

It is recognized that from any small series of cases absolute conclusions are scarcely justified. However, it would seem apparent from this study that re-evaluation of the surgical treatment of this disease is indicated. Pemberton *et al.*[19] and Smithwick[17] have shown that measures short of resection yield exceedingly poor late results and that many patients so treated must retain a permanent colostomy to remain free from symptoms. This is a serious matter to consider in dealing with a benign lesion. Smithwick[17] further pointed out that surgical intervention other than resection, including colostomy, does not lower the late mortality due to the disease. The operative mortality for resection reported by these authors is low. That of Pemberton and his associates[19] (2.7 per cent) is particularly significant since it represented a large series treated after 1940. This reduced mortality was approximately one-half that which they reported for resection of malignant lesions of the large intestine during the same period. In the present series there was no operative mortality and no late mortality due to the disease.

The cure rate following resection is infinitely better than after less radical surgery. Smithwick[17] reported 84 per cent of cases living and well, one to ten years following resection, while Pemberton *et al.*[19] stated that approximately 80 per cent were cured. In the present series, 95.6 per cent were well, one to 16 years after resection. In view of these facts it seems obvious that a bold attack on the complicated case of sigmoid diverticulitis is not only justified but definitely indicated. Once surgery becomes necessary, resection should be the ultimate goal.

The present review not only confirms the above conclusions but raises certain other questions for rediscussion. The great majority of the 32 cases undergoing resection were operated on promptly after preliminary study. As previously indicated, three cases required resection after less definitive operation failed. Two of these patients had recurrent acute attacks and were primarily resected promptly upon readmission for the acute recurrence. The

other underwent primary resection for a fecal fistula which followed drainage of an abscess. Of the total cases, 25 were primary resections, preliminary colostomy being performed in the remaining seven. The average duration prior to resection of six of these colostomies was four weeks, the longest nine weeks, in contrast to the customary delay of three to 12 months. The resultant reduction of morbidity was striking. The average total duration of all colostomies, including those resulting from obstructive resections (excluding permanent colostomy in one patient) was only nine weeks. The dictum that colostomy should be maintained three to 12 months prior to definitive surgery is certainly open to question.

This radical departure from accepted teaching will undoubtedly be questioned. After reviewing the case records and in light of present concepts, the author believes that some of the patients might have been treated with greater safety had preliminary drainage or colostomy been instituted, delaying the attack on the diseased segment until more adequate preparation of the patient had been accomplished. However, serious criticism of the treatment employed is scarcely justified in view of the results obtained.

In the light of the series of cases under discussion it would seem reasonable to outline a plan of therapy which will afford the patient stricken with severe and complicated diverticulitis of the sigmoid colon the safest opportunity for early recovery. One must conclude that preliminary colostomy in many cases is not only unnecessary but contraindicated considering the prolonged morbidity which it induces. Obviously, when complete obstruction complicates the disease diversion of the fecal stream is required. It commonly may be necessary when previous drainage of an abscess results in a fecal fistula. It is often indicated in general peritonitis resulting from acute perforation of a diverticulum of the sigmoid. It may be advisable for vesicosigmoidal fistulas which follow operation or are associated with pelvic abscess. However, spontaneous vesicosigmoidal fistula, in the absence of obstruction or abscess, need not necessarily demand colostomy. In the present series, two patients with this complication were treated by primary resection without colostomy. Both were discharged from the hospital on the seventeenth postoperative day, and have remained well two years and two months, and one year, respectively. When colostomy is indicated, it should be made at the level of the transverse colon. Sigmoid colostomy will seriously impede future resection.

An abscess following perforation of a diverticulum may resolve with antibiotic and chemotherapeutic treatment. However, many will require drainage. To delay operation in the hope that spontaneous drainage into adjacent bowel will take place as suggested by Hayden[26] is nothing short of procrastination. Transverse colostomy, as an adjunct to drainage, is indicated if obstruction is associated. Some cases will subside completely following simple drainage. However, those with persistent symptoms and certainly those with resultant fistula should be subjected to resection.

Cases not presenting the above complications may require operation because of suspected carcinoma or because of recurring acute episodes. The acute attack will generally subside with conservative management, including antibiotic and chemotherapeutic measures. Thereafter, with the bowel adequately prepared, exploration may be undertaken with the view toward primary resection. This commonly can be performed with safety.

When one is faced at the operating table with the disquieting realization that a suspected pelvic tumor is in reality a sigmoid or rectosigmoid diverticulitis, obstructive resection should be considered, depending upon the location of the lesion. With involvement of the rectosigmoid, primary resection and anastomosis with complementary transverse colostomy may seem a wise choice, depending upon the state of bowel preparation.

When resection is undertaken, the bowel should be divided several inches from the zone of inflammation to insure safe anastomosis and to avoid the complications which appear to follow the removal of a short segment. The type of anastomosis, aseptic or open, seems of little consequence provided the method chosen yields a wide stoma.

It is doubtful that complementary cecostomy is of any real value. If for any reason the integrity of the suture line is in question, complete sidetracking of the fecal stream is a much safer procedure. If, however, the anastomosis is not in doubt, cecostomy would seem unnecessary and merely complicates the postoperative course.

SUMMARY

A review of 20 years' experience (1929 to 1949) at The Portland Clinic in the surgical treatment of diverticulitis of the colon has been presented. A total of 38 cases have been tabulated. Three right colectomies have been performed for perforation of diverticula of the ascending colon and cecum. Thirty-two of 35 patients with diverticulitis of the sigmoid and rectosigmoid have undergone resections of the involved segment. Twenty-five primary resections and seven resections after preliminary colostomy are included. No operative mortality occurred.

Twenty-two of 23 cases (95.6 per cent) of sigmoid resections, followed one to 16 years, are classified as living and well. There has been no late mortality from the disease. All colostomies have been closed except in one patient who, because of persistent vesicosigmoidal fistula which recurred after repeated resections, carries a permanent colostomy.

The great reduction in morbidity in this series compared to other reports has been striking. The average duration of colostomy prior to resection was four weeks, while total duration of colostomy (excluding one permanent colostomy) averaged nine weeks.

In view of the low mortality following resection and in view of the high morbidity, high recurrence rate, and late mortality which follow less radical measures, a bold approach to this problem deserves serious consideration. Re-evaluation of the surgical therapy in complicated sigmoid diverticulitis is indicated.

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CARCINOMA OF THE GALLBLADDER
A CLINICAL AND PATHOLOGIC ANALYSIS OF FIFTY CASES*

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WELL DOCUMENTED PAPERS on the subject of carcinoma of the gallbladder very properly emphasize the grave prognosis of this disease. It seems justifiable, therefore, to continue to analyze large series of cases in the hope that a more effective approach in its treatment may be devised.

The present report is concerned with 50 cases of carcinoma of the gallbladder among which 15 patients died without operation but were examined at autopsy; 15 had operations upon their biliary tract and then later came to autopsy; and 20 had operations with the removal of tissue for pathologic examination but no autopsy examinations. Thirty of the cases represent the total number of instances in which cancer of the gallbladder was found in a series of 8808 autopsies performed at the Pathological Institute, McGill University, and 35 of the cases were comprised in a series of 3000 consecutive operations on the biliary tract performed at the Royal Victoria Hospital, Montreal, during the period 1926 to 1948. Thus, the incidence of carcinoma of the gallbladder is 0.34 per cent in the autopsy series and 1.16 per cent in the surgical series. The frequency of occurrence of this type of cancer in the present series as compared with the incidence reported in other communications is shown in Table I.

An analysis of Table I also shows clearly that the disease has a marked tendency to occur more frequently in women than in men. Ewing[6] states that carcinoma of the gallbladder is four to five times as frequent in females as in males. The figures of Willis[27] would indicate that women are affected more frequently than men, in a ratio of three or four to one. In the series reported here there were 36 females and 14 males.

Cancer of the gallbladder is also essentially a disease of the older age group, occurring nearly always after the age of 50. A moderate number of cases have been reported in relatively young persons and in Biering's recent report[1] the patient was a 13-year-old girl. Moxon[16] is often cited as having reported a case in which the patient was four years old. He is misquoted, for in his original paper he did not give the patient's age, but in fact, described his occupation as that of a brushmaker. None of the patients in the series of this paper was under 40 years of age. The oldest was 85 years (Table II).

Gallstones were present in 82 per cent of the total cases. No mention was made of their presence or absence in 16 per cent, and in one case, 2 per

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cent, it was definitely stated that none could be found. These figures approximate closely those reported in the literature (Table III).

TABLE I.

	Number of Autopsies	Incidence (Per Cent)	Number of Operations on Biliary Tract	Incidence (Per Cent)	Total Number of Cases	
					Female	Male
Finney[7]	.....	....	1,192	1.5	16	2
Warren and Balch[26]	.....	....	1,528	1.96	..	..
Vadheim, Gray, and Dockerty[24]	.....	....	33,500	0.87	..	..
Hochberg and Kogut[9]	1,074	0.36	1,078	2.5	25	6
Jankelson[11]	11,400	0.42	.....	....	28	20
Cooper[4]	2,941	0.61	1,500	3.0	..	..
Author's series	8,808	0.34	3,000	1.16	36	14
Total	24,223	0.41	41,798	1 07	105	42

ETIOLOGY

The etiology of cancer of the gallbladder is unknown. The frequent association of stones with cancer of the gallbladder has been taken as evidence that cholelithiasis is the predisposing factor in its development. Support for this view is derived in part from the studies of Kazama[13] in 1922, and Leitch[14]

TABLE II.—*Number of Cases.*

Age (Years)	Liebowitz[15]	Finney[7]	Sainburg[19]	Author's Series	Total
30–39	..	..	1	..	1
40–49	3	1	8	9	21
50–59	8	3	29	18	58
60–69	7	6	30	12	55
70–79	8	7	6	10	31
80–89	2	1	1	1	5
Average age	64.1	67.4	60.1	59.1	61.3

in 1924, both of whom inserted hard foreign bodies, including gallstones removed from human beings, in the gallbladders of guinea pigs. They reported that 26 of 98, and eight of 35 animals, respectively, developed carcinoma of that organ. These experiments were fully reviewed by Burrows[2, 3] who also carried out experiments with gallstones (human) and with pellets, some

TABLE III.—*Incidence of Stones in Cancerous Gallbladders.*

	Percentage
Judd and Gray[12]	64.6
Shelley and Ross[21]	73.7
Hochberg and Kogut[9]	76.0
Illingworth[10]	81.5
Warren and Balch[26]	88.0
Author's series	82.0

containing cholesterol, others dibenzanthracene, and still others, fat. He obtained inflammatory proliferations of a benign type, but no tumors. He concluded that this had been the case also with the results of the earlier workers. Creighton[5] is of the same opinion, that the changes described by

Kazama and Leitch were merely those of inflammatory hyperplasia. Willis,[27] in his discussion of Burrows' work, further pointed out that the guinea pig is an animal which seldom develops spontaneous tumors and which is also refractory to the experimental production of skin tumors. Petrov and Krotkina[17] have recently reopened the discussion. They reported experiments on 100 animals in which five cases of carcinoma resulted from the introduction of foreign bodies into the gallbladder. Fifty-one of the 100 guinea pigs survived 14 months or longer. In five of these 51 animals, after 14 to 39 months, there was found an epithelial proliferation of the gallbladder wall with characteristics of malignant growth, including local invasion and distant metastases. Gallstones were used as the foreign body in four of the surviving 51 animals. None of these developed cancer. In eight other subjects the foreign body was a glass tube containing one gamma of radium. Two of these animals developed malignant tumors. Ten sterile glass tubes, each measuring 16 by 2 mm., were placed in each gallbladder of the remaining 39 guinea pigs. Petrov and Krotkina were aware of the work of Kazama and Leitch, and of the criticism directed toward these earlier workers, and although they attempted to perform a more carefully controlled experiment, it would appear that they invalidated their results to some extent by using a radioactive material as one of the test substances.

Both Graham[8] and Sainburg and Garlock[19] feel that the published statistics and experimental data are convincing enough to accept as fact that cholelithiasis is the most important precursor of carcinoma and go on to advocate cholecystectomy as a prophylaxis against the development of cancer. Sainburg and Garlock, in particular, argue that the mortality due to malignant transformation, in addition to the other frequently fatal complications of cholelithiasis, impose an obligation to remove all calculous gallbladders, in the absence of surgical contraindications. They cite the mortality figure of 1.6 per cent following cholecystectomy reported by the Mayo Clinic,[25] the 1.5 per cent of Graham,[8] and the 0.6 per cent mortality rate in 346 cholecystectomies performed during 1946 at the Mount Sinai Hospital.[19]

Warren and Balch,[26] writing in 1940, thought otherwise. It was their belief that although simple cholecystectomy carried a mortality not greater than 2 per cent, it was not enough lower than the risk of carcinoma, 1 to 2.5 per cent, to say flatly that cholecystectomy should be performed in all cases of stones for that reason alone. They estimated that the policy advocated by Graham and others would involve performing cholecystectomies on 25 to 50 per cent of the female population over 60 years of age.

One concludes from the conflicting experimental results reported above that further attempts to produce cancer of the gallbladder should be made, particularly on other species of animals. Since the exact etiology of carcinoma of the gallbladder is as yet unknown, and since the mortality figures for cholecystectomy and the incidence of cancer of the gallbladder vary slightly from clinic to clinic, the value of cholecystectomy solely as a prophylaxis against the development of cancer in that organ remains a personal decision.

CLINICAL FEATURES

A striking fact which becomes immediately apparent upon reviewing the clinical histories of the 50 cases in this report was that 66 per cent of the patients experienced the initial onset of their illness six months or less prior to their entry into the hospital. Before that time they had enjoyed relatively good health. Warren,[26] Seide and Geller,[20] and Jankelson[11] have all remarked on this same point, each reporting approximately the same duration of symptoms. The majority of the remaining patients gave histories which may be described as typical of chronic gallbladder disease, that is, of cholecystitis or cholelithiasis, extending over a period of years. Two patients had no symptoms ascribable to the biliary tract, both dying of cardiac disease. Their tumors were incidental findings at autopsy.

The symptoms which led the group of patients with short histories to seek medical attention may be reviewed in order of frequency of occurrence.

Jaundice, suddenly and rapidly established and persistent, occurred in 70 per cent of the cases. But it must be pointed out that it was also often late in its appearance, sometimes becoming apparent in the few days prior to admission. Ten per cent of the remaining patients had a history of jaundice at some time or other in the past.

A history of weight loss varying from 10 to 45 pounds was obtained in 70 per cent of the cases. It was almost always volunteered by the patient and described as occurring during a period of a few weeks to a few months.

Constant pain was a frequent complaint. It was recorded in 66 per cent of the cases and was most commonly localized in the right upper quadrant, less often in the epigastrium. It was described as ranging in severity from moderate to marked and only in its very early stages as being occasionally relieved by belching.

In 62 per cent of the cases there was recorded tenderness on palpation of the upper abdomen and in 23 patients, or 45 per cent, a mass was felt. The liver edge was frequently palpable as low as three to four finger-breadths below the costal margin. The moderately tender mass lay beneath the liver and could be made out by patient and physician alike. It varied slightly in size from patient to patient, averaging approximately 8.0 cm. in diameter.

Anorexia and vomiting were present in 40 per cent of the patients. These symptoms were, at first, intermittent; then they slowly became more regular in appearance and accounted, no doubt, for a large part of the rapid, severe, weight loss described above.

Ascites developed in 38 per cent of the patients.

The cachectic stage was marked by fever from infections, massive replacements of liver tissue by tumor, emaciation and hemorrhages. The bleeding resulted from invasion or ulceration of blood vessels by tumor or stones, or was due to disturbances in the blood clotting mechanism.

The histories of the majority of the patients who gave a long history of abdominal complaints differed from the above group in several respects. While

they gave a remote history, 5 to 20 years, of attacks of colic and jaundice suggestive of cholecystitis or cholelithiasis, they had, to judge from the patients' descriptions, a recent recurrence of pain, loss of weight, vomiting and jaundice, all of which were more constant, more severe, better localized, and less easily relieved, than they had been previously. Even those patients who were having symptoms rather regularly during the antecedent year or two complained of this rather explosive change in the character and severity of their symptoms.

Four patients described a period of one or two weeks of abdominal distress, then the abrupt appearance of anorexia and vomiting to be followed in a day or two by jaundice. At operation tumor tissue was found to be the cause of the common duct obstruction.

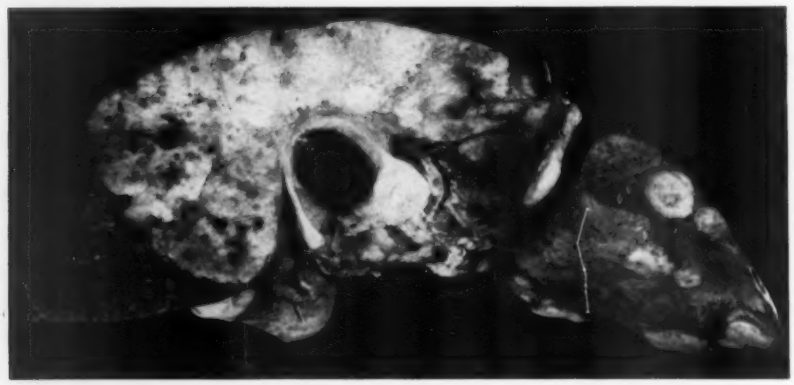

FIG. 1.—Carcinoma of the gallbladder with direct extension and metastatic spread to liver.

PATHOLOGIC FEATURES

One can conclude from observations made at the autopsy table that the primary growth tends to assume one of two forms, though gradations from one to the other may be found. These different forms were dependent, in part, upon the degree of cellularity of the tumor, the abundance of supporting stroma and the presence or absence of associated infections. In most instances the gallbladder was largely replaced by a solitary, hard, fibrous, shrunken, tumor mass. Occasionally, however, the primary growth was medullary instead of fibrous in character, and a very large, bulky, gallbladder distended either by tumor, mucoid material, or pus presented itself. Less commonly the organ was perforated and an abscess had formed, the walls of which were made up of parts of the stomach, pancreas, colon, duodenum or liver.

The former type of primary growth was stony-hard on section. The gallbladder which was firmly imbedded in the mass was thickened and contracted down over its contained stones. It was also generally firmly adherent to the adjacent liver due to extension of tumor into the liver bed (Fig. 1).

If the tumor was more cellular, as in the latter type, the gallbladder was relatively soft in consistency and distended. Its wall was very greatly thickened, rubbery soft to rubbery firm in consistency, and white in color. The presence of some sort of tumor was often suspected on gross examination. If infection had developed or portions of the growth had become necrotic, section would reveal a mass of tumor tissue with a central area of putrefaction or necrosis with all, or almost all, of the gallbladder wall totally destroyed. Its former position was marked by one or two stones lying in a small cavity. In a few instances the tumor had a gelatinous mucoid character. Fistulas between gallbladder and common duct or stomach or duodenum occurred in a few cases in both main types.

One patient who was admitted in a moribund condition died one hour later. Her family stated that she had been in apparent good health until three weeks before admission, when she began to complain of rather severe crampy abdominal pain. Twelve hours before admission she had experienced a massive hematemesis and collapsed. Autopsy revealed an extensive cancer of the gallbladder with a freshly formed fistula, apparently caused by the erosion of a stone, between the gallbladder and duodenum, with ulceration and perforation of a large blood vessel.

The carcinomatous growth was too extensive in a large majority of patients for one to decide the probable site of origin. In the few instances in which some sort of estimate was attempted, fundus or neck were thought to be the usual sources.

The various surgeons' descriptions of their findings at operation in the cases which did not come to autopsy bore a very close resemblance to the situations found in those that had postmortem examination. The exceptions occurred in a few patients in whom the primary growth was still at an early stage and resection was possible.

HISTOLOGIC TYPES

Carcinoma of the gallbladder, in general, occurs in four main histologic types. Representative examples of all were found in this series. The most frequent were the scirrhous and medullary types (Fig. 2). Typically, they were characterized by neoplastic acini occurring in groups or singly, scattered through a fibrous connective tissue stroma. The lining cells were cuboidal to columnar, with basally placed nuclei and relatively clear cytoplasm. Imperfectly formed alveoli were frequent. The neoplastic tissue usually had invaded all layers of the gallbladder and extended into neighboring structures. The tumors termed scirrhous were quite similar in appearance to those called medullary and differed only in possessing a more extensive growth of dense connective tissue with a slightly sparser distribution of neoplastic epithelium.

A less common form of cancer was the papillary adenocarcinoma (Fig. 3). Here, the mucosa of the gallbladder was thrown up into numerous branching papillary projections covered by frankly neoplastic epithelial cells. These

FIG. 2

FIG. 3

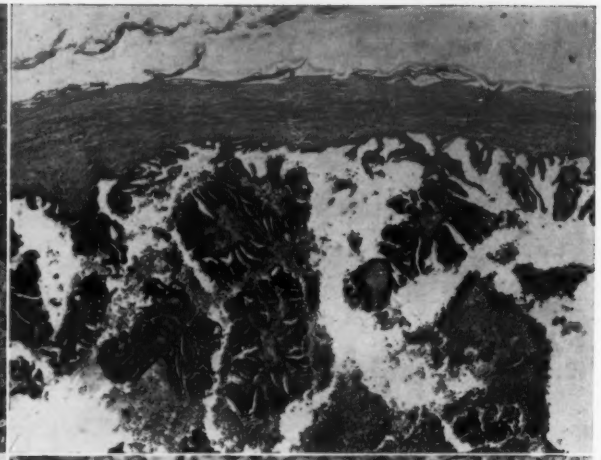

FIG. 4

FIG. 5

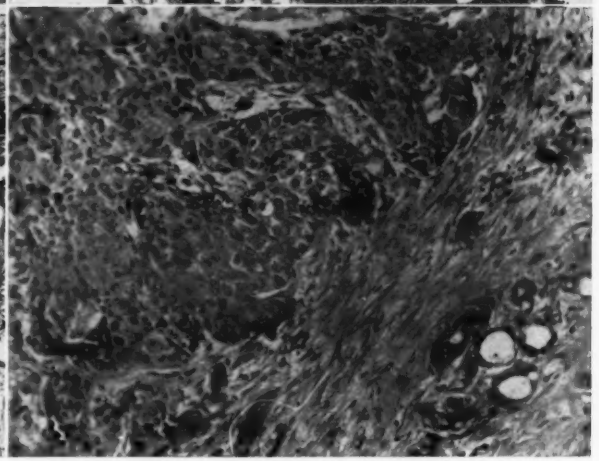

FIG. 2.—Photomicrograph of carcinoma of the gallbladder, scirrhous type. x 16.
FIG. 3.—Photomicrograph of carcinoma of the gallbladder, papillary type. x 24.
FIG. 4.—Photomicrograph of carcinoma of the gallbladder, mucoid type. x 16.
FIG. 5.—Photomicrograph of carcinoma of the gallbladder, squamous type. x 120.

were columnar to tall columnar with centrally to basally placed nuclei. The tumor tended to grow out into the lumen as well as invade the muscular and serosal coats. In some instances the tumor formed small alveoli deep to the muscular layers, presenting a picture resembling Rokitansky-Aschoff sinuses or cholecystitis glandularis cysticum. However, the malignant features of the individual cells and the histologic pattern in sections taken elsewhere from the organ revealed their true nature.

Sometimes parts of the tumor, or, in a few rare instances, the whole, secreted an abundant amount of mucoid material. In addition to the marked distention of the lumen with this material the cells themselves were often scattered as single acini or clusters of acini in a loose fibrous stroma, the intervening spaces being filled with mucus. A few cells retained the mucoid material within their borders, producing a vacuolated cytoplasm (Fig. 4).

In three cases the dominant histologic form was squamous cell carcinoma in which there were small areas of adenocarcinoma. Kerato-hyaline changes were frequent and at one or two points actual pearl formation was attempted. The supporting connective tissue was abundant.

Sections of gallbladder which were taken at a distance from the area of tumor showed evidence of chronic cholecystitis in every instance. Monocytes, plasma cells and lymphocytes were focally and diffusely distributed throughout all layers, along with an actual increase in the fibrous tissue stroma.

The frequency of occurrence of the different types of growth were as follows: 42 per cent scirrhous; 30 per cent medullary; 18 per cent papillary; 6 per cent squamous; and 4 per cent mucoid.

Fig. 3.—Photomicrograph of carcinoma of the gallbladder, mucoid type. × 16.
Fig. 4.—Photomicrograph of carcinoma of the gallbladder, squamous type. × 120.

MODE OF SPREAD

The spread of carcinoma of the gallbladder is by direct extension into the neighboring tissues and by way of the lymphatics. Rarely does it extend by the way of blood channels or transperitoneally. The opportunities for local and distant spread by direct extension and via lymphatics are many, both because of the absence of a peritoneal covering separating the organ from the liver and of the luxuriant lymph plexuses draining the gallbladder.

In the cases being reviewed, local extension into the liver was a common method of dissemination. It occurred in 36 of the 50 cases, making it impossible to dissect the gallbladder free from its bed.

The gallbladder possesses two plexuses of lymph channels, one in the subepithelial layer and the other in the subserosal layer. These two plexuses communicate by way of numerous short anastomotic branches which perforate the muscular layers. The subserosal plexus in turn empties into several main vessels which follow the cystic artery to the neck of the organ and to the cystic node. From there, the lymphatics extend chiefly to the chain of mesenteric nodes which lie beside the common duct and portal vein up to the hilus of the liver. There also exists an intimate connection between the lymphatics of the liver and those of the subserosal layer of the gallbladder (Cooper,[4] Poirer and Charpy,[18] and Sudler[23]).

The cystic node and periportal lymph nodes were affected in over three-fourths of the cases. Small masses of tumor averaging 1 to 4 cm. in diameter were found deep in the liver substance in almost as many cases. The omentum and the peritoneal surfaces were studded with smaller masses of tumor in one-third of the patients.

The presence of lymphatic spread, but no local extension, was demonstrated at autopsy or operation in eight cases. During one other operation the surgeon became aware that he was dealing with a cancer and following resection of the gallbladder he made a careful search of the operative field, but no tumor was found elsewhere.

Pulmonary metastases were found in six cases, in one of which there was gross pulmonary embolism in the form of a mass of tumor tissue. Adrenal glands and pleurae in one case, and the lumbar vertebrae and angle of the jaw in another, were also sites of metastases. The presenting symptoms of the latter patient had been pain in the jaw and back, and weight loss.

Obstruction of the bile drainage occurred in one of three ways. Large tumor masses extending directly down from the neck of the gallbladder and compressing the cystic and hepatic ducts was one. Occlusion of the hepatic duct by enlarged periportal lymph nodes was another. Infrequently there was actual invasion and plugging of the common duct.

DISCUSSION

In the cases analyzed here a correct preoperative or antemortem diagnosis of carcinoma of the gallbladder was rarely made. The majority of other reviews of the subject describe a similar situation. In the present series of cases the marked prominence of colicky pain, or cachexia with obstructive jaundice, or a palpable mass with an enlarged liver, seemed to be the clinical features most often leading to an erroneous diagnosis of cholecystitis and cholelithiasis, or carcinoma of the head of the pancreas, or primary or metastatic carcinoma of the liver respectively. The actual occurrences of some of these diseases during the same 23-year period covered in this report were: carcinoma of the Ampulla of Vater four times; carcinoma of the bile ducts 28 times; carcinoma of the head of the pancreas 35 times; and primary carcinoma of the liver 16 times.

An attempt was made to determine whether any degree of correlation existed between the symptoms that led these patients first to seek medical attention, and the extent of the primary growth found at the time of operation. The following impressions were obtained. Firstly, those patients who complained of constant, severe pain almost always had tumors which were non-resectable. Secondly, marked weight loss was another, though somewhat less, constant feature, indicating local and distant invasion and metastases. And, thirdly, the presence of a palpable mass was not necessarily associated with a non-resectable lesion, for while the palpable mass often represented omentum, gallbladder, and colon or stomach all matted together, not uncommonly it proved to be merely an inflamed gallbladder distended with bile, pus

or tumor, the tumor being grossly restricted to the organ. Metastases to the regional lymph nodes might have been present, but resection of the gallbladder was technically feasible.

In the total series of 50 cases, 26 per cent of the patients were too ill to withstand an operation. Forty-eight per cent were operated upon but the tumor was found to be not resectable. Resection was possible in 14 per cent of the cases, but after careful search the surgeon found distant extension of the tumor in all but one case. In 8.0 per cent of the cases the operator was unaware that he was dealing with a cancerous gallbladder and made no search for regional lymphadenopathy or metastatic lesions. These 8.0 per cent were unfortunately also lost to follow-up. Two cases, or 4 per cent, of very early cancer of the gallbladder confined to the organ were incidental findings at autopsy in two patients, one of whom died of cardiac disease, the other of cancer of the urinary bladder.

The minimum mortality rate of 88 per cent in this series of cases approximates those described elsewhere in the literature. Of Smithies'[22] 23 cases, 21 died immediately or within eight months after operation. Only two patients were alive at the end of four years. In Cooper's[4] series of 48 cases there was a possible cure in only one case. Sainburg and Garlock[19] considered the disease incurable, reporting a mortality of 98.5 per cent in less than three years after operation in 75 cases.

SUMMARY

Fifty cases of carcinoma of the gallbladder have been analyzed. The dismal prognosis described by other authors was found to hold for this group as well. Sixty-six per cent of these patients experienced the onset of their illness six months or less prior to hospital admission, and the majority of the remaining patients described a recent abrupt increase in the severity of long-standing symptoms. The mortality rate in the total series was at least 88 per cent, indicating that carcinoma of the gallbladder is still a virtually incurable disease. A brief comment has also been made on some of the current theories of the etiology of cancer of the gallbladder.

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PRIMARY CARCINOMA OF THE GALLBLADDER

REPORT OF 29 CASES*

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REPORTS[1, 2] ON CARCINOMA of the gallbladder show an associated cholelithiasis in from 86 per cent[3] to 100 per cent[4] of the cases. Gallstones could result from the carcinoma, or they could be precursors of the malignant condition. Metastatic carcinoma of the gallbladder does not appear to be associated with an increased incidence of cholelithiasis;[5] most reports show that from 50 to 70 per cent[5] of patients with carcinoma of the gallbladder have a past history of gallbladder disease. These facts indicate that cholelithiasis precedes carcinoma of the gallbladder and may be an etiologic factor.

Some authorities[3, 6, 7] advocate cholecystectomy in the presence of asymptomatic gallstones as a means of preventing carcinoma. They believe that the dangers and complications of gallbladder surgery are less serious than the possibility of the patient developing cancer. Other investigations[8-10] stress the extremely low incidence of carcinoma of the gallbladder in comparison to the high incidence of cholelithiasis, and therefore do not urge operation for the "silent gallstone."

The incidence of cholelithiasis from autopsy material has been reported to be from 8.4 per cent to as high as 32.5 per cent—50 per cent were found after the seventh decade. This evidence indicates to us that removal of the gallbladders in from 8.4 to 32.5 per cent of the people as a means of attempting to reduce the incidence of cancer of this organ is a questionable procedure.

Comfort, Gray, and Wilson[10] reported 112 patients with asymptomatic gallstones who refused cholecystectomy, and who were observed from ten to 25 years. Not one developed carcinoma of the gallbladder, although six of them did develop carcinoma elsewhere. More follow-up studies of this nature, observing the course of patients with asymptomatic gallstones, are clearly indicated.

Reports of operations for carcinoma of the gallbladder show that either patients are inoperable or that surgery did not appreciably prolong the life of the patient. Cures have been effected in only about 2.5 per cent of these patients.[5] Mattson,[9] as an example, reported no cures in 63 cases. The only exception to the uniformly low cure rate is that of Vadheim *et al.*,[14] who reported five-year survivals in 13 patients with cholecystic carcinoma of Broders' Grade One.

Carcinoma of the gallbladder presents several medical problems. First, the relationship of cholelithiasis to carcinoma of the gallbladder seems well established by previous reports. A second problem is whether greater familiarity

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with the usual clinical findings in these patients would result in more frequent and earlier diagnosis of this condition. Third is the question of the removal of asymptomatic gallbladder with cholelithiasis as a preventive measure for the subsequent development of carcinoma, and fourth, how treatment of this condition can be improved.

1. Incidence. The ratio of carcinoma of the gallbladder to cholelithiasis is impossible precisely to determine. Not every patient seen at the Clinic has a cholecystogram: hence the overall frequency of cholelithiasis is not accurately known. Furthermore, every patient with cholelithiasis does not have a cholecystectomy, and therefore the ratio of carcinoma of the gallbladder in patients who have had cholecystectomies is not necessarily an accurate reflection of this relationship.

Between 1932 and 1948 inclusively there have been 29 cases of carcinoma of the gallbladder operated on at the Cleveland Clinic. In the same period there have been 1488 cholecystectomies done. The incidence of carcinoma in relation to the number of cholecystectomies is therefore 1.9 per cent in this series. However, it must be remembered that most of the patients in whom cholecystectomies were not done were asymptomatic and had "silent" gallstones. Since carcinoma of the gallbladder is preceded by symptoms, it is probable that there were few if any patients with carcinoma in the unoperated group. The patient with carcinoma of the gallbladder is ill, and some operative procedure resulting in the diagnosis of the condition is usually done.

During the same time 350,000 new patients have been seen at the Clinic. Lam[16] reported 34 cases in a group of comparable size. The very fact that only 29 cases of carcinoma were found at operation suggests the relative rarity of this type of cancer.

During this same interval, a diagnosis of cholelithiasis by roentgen-ray examination was made in 4459 patients. The incidence of carcinoma of the gallbladder in relation to the incidence of cholethiasis as determined by roentgen-ray examination is calculated to be 0.66 per cent. This indicates that cancer of the gallbladder is a relatively uncommon disease, whereas cholelithiasis is common, the ratio being 154 to 1.

The true incidence of carcinoma of the gallbladder in patients with cholelithiasis is almost certainly much lower than 0.66 per cent, since many patients with asymptomatic gallstones did not have cholecystograms. The autopsy incidence of cholelithiasis (8.4 to 32.5 per cent) has already been cited. Bockus[5] estimates the incidence of cholelithiasis to be 10 per cent. On this basis, with 350,000 new patients seen during this time, many patients with asymptomatic gallstones evidently did not have cholecystograms and the diagnosis of gallstones was not made. Consequently, the true ratio of neoplasm to calcareous disease of the gallbladder is probably actually less than the figure (0.66 per cent) previously cited.

Cholecystectomy still carries with it some mortality and morbidity. The operative mortality for cholecystectomy probably exceeds the incidence of carcinoma of the gallbladder. We believe that more lives would be lost postopera-

tively by routine cholecystectomy in the presence of asymptomatic gallstones than would be lost, years later, by the subsequent development of cholecystic carcinoma. It must also be remembered that the patient who dies postoperatively does so immediately, while the patient who develops neoplasm of the gallbladder will probably not do so for a considerable length of time.

The age and sex incidence in our series is presented in Table I. The sex ratio was four women to one man. No case occurred in a patient under 40 years of age, while 21 of the 29 cases were in patients over 60 years of age.

TABLE I.—*Age and Sex Distribution.*

Age	Female	Male	Total
40-49	1	1	2
50-59	6	0	6
60-69	9	5	14
70-79	7	0	7
Total	23	6	

2. History. A history of pre-existing biliary colic was obtained from 17 patients, antedating the present illness by nine months to six years. A consensus of reports[5] indicates that from 50 to 70 per cent of patients have a past history of benign biliary disease.

TABLE II.—*Symptoms in Primary Carcinoma of the Gallbladder.*

Symptom	Number of Cases	Average Duration of Symptom
Weight loss	23	5.5 months
Pain	21	3.5 months
Constipation	21	3.6 months
Nausea or vomiting	16	2.5 months
Jaundice	16	5.4 weeks
Anorexia	16	2.5 months
Dyspepsia	13	3.5 months
Weakness	10	5.5 months
Mass in abdomen	4	5 months
Fever and chills	3	2.2 months
Anemia	1	8 months
Hematemesis	1	6 weeks

The presenting symptoms in our series are tabulated in Table II. Weight loss and weakness were the earliest symptoms. Weight loss was present in 23 cases, the average loss of weight being 22 pounds in 5.5 months. Mattson[9] found that 70 per cent of his patients lost an average of 27.5 pounds. It is significant that Vadheim *et al.*,[14] in their series of early carcinomas in which no preoperative diagnoses were made, found that 67 per cent suffered loss of weight.

Pain was also an early and important symptom. Twenty-one patients complained of pain as a predominant symptom. In other series[3, 4, 7, 9, 17-19] pain has been reported in about 80 per cent. The pain was described as a dull ache located in the epigastrium in ten patients, in the right upper quadrant in nine

patients, and solely in the lower abdomen in two patients. Characteristically it began as colicky or cramplike pain in 11, then rapidly assumed a constant nature in ten patients. Radiation of pain occurred in half of the cases, spreading to the scapula, back, shoulder, chest, and in one patient to the left breast. The pain was usually of moderate severity. The average duration of this symptom was 3.5 months.

Jaundice was present in 16 cases. In a few patients it was the first symptom drawing attention to the biliary tract. The average duration of the jaundice in our series was five weeks, identical with the findings of Cooper. In all of our patients the jaundice was of the continuous, obstructive type. Jaundice most commonly was caused by obstruction of the common duct; rarely is the jaundice caused by liver metastases. Painless jaundice was present in only five patients.

Anorexia, nausea, vomiting or all three were found in 16 patients, of whom 12 also had jaundice. In no case did these symptoms, or that of dys-

TABLE III.—*Physical Findings in Carcinoma of the Gallbladder.*

Finding	Number of Cases
Palpable liver	22
Palpable gallbladder or mass	17
Nodular or hard	16
Fluctuant	1
Jaundice	16
Tenderness	14
Ascites	2
Elevated temperature	2
Metastatic lesion in skin in inguinal region	1

pepsia, antedate the weight loss, pain or jaundice. In addition to the symptoms mentioned, one patient complained of frothy stools, one of pyrosis, and one of diarrhea. Anemia constituted the chief complaint in one patient.

3. Physical Findings. In Table III, it will be seen that 22 patients had a palpable liver which was usually over 4 cm. below the costal margin. In other reports the incidence of this finding varies but little from 50 per cent; however, Vadheim, *et al.*[14] noted a palpable liver in only 23 per cent. A palpable mass was present in 17 patients and was found in each case to represent either the carcinomatous gallbladder or direct invasion of the liver. In no patient was the abdominal examination negative, but in three patients there was a single finding of tenderness or distention.

4. Laboratory Findings. Routine laboratory findings were usually noncontributory. Anemia is not a characteristic feature in this type of cancer. The average hemoglobin in 23 women was 12.5 Gm. per 100 cc., and the average in six men was 11.7 Gm. per 100 cc. The hemoglobin was below 12 Gm. in seven patients, and less than 11 Gm. in four patients. One man had a hemoglobin of 6.9 Gm.; he was found to have a pyonephrosis secondary to adjacent metastases. The leukocyte count was normal except in two patients who had a count of 20,000 per cu. mm. Prothrombin times were done in 13 patients, averaging 74 per cent.

Little mention is made in the literature regarding liver function tests in carcinoma of the gallbladder. Lam[16] had two patients with bromsulfalein retention, each of whom had liver extension. In our series, bromsulfalein retention was determined in four patients. Three patients without jaundice had definitely positive tests; these patients were found to have liver metastases, invasion of the portal vein, or invasion into the liver. The fourth patient had a normal test, but did have invasion of the liver.

5. *Roentgen Ray Findings.* Cholecystograms were done in 16 cases, all of which revealed non-functioning gallbladders. Twenty-three plain gallbladder films were done, disclosing three cases with opaque stones and one case with a calcified gallbladder. Reports of a normally functioning gallbladder in the presence of cholecystic cancer are indeed rare in the literature, and we have been unable to find any report of the tumor being visualized through cholecystographic dye, as is possible with a papilloma of the gallbladder.

Pressure from extension of the tumor may reveal defects in the roentgen ray examination of adjacent organs. Three patients in our series had pressure defects on the stomach or duodenum as determined by barium meal examination. Urologic examinations demonstrated pyonephrosis in one patient with metastases to the right adrenal gland, and hydronephrosis in one patient with metastases to the retroperitoneal space.

6. *Diagnosis.* It is frequently stated that a preoperative diagnosis of carcinoma of the gallbladder is seldom made; Danzis[4] and Vadheim, *et al.*[14] found that none in their series had been diagnosed preoperatively. Sainburg and Garlock[7] stated that 23 per cent in their series were diagnosed preoperatively. Correct preoperative diagnoses were recorded in eight cases in our series. In many cases the operation was performed because of mistaken diagnoses of carcinoma of the pancreas or ducts, cholelithiasis, carcinoma of the stomach, and common duct stone. However, two of Lam's[14] cases, and one of ours carried a diagnosis of cirrhosis of the liver for a period prior to operation.

Carcinoma of the gallbladder should be suspected particularly in women over 60 years of age who give a history of biliary colic during the past three years, and who complain of epigastric or right upper quadrant pain of three months' duration, and with weight loss of approximately 20 pounds. Vomiting and constipation are frequently present. If the patient is jaundiced this is the latest symptom to appear. The presence of a palpable liver and/or a mass in the right upper quadrant, together with a non-functioning gallbladder on roentgen ray study should suggest this diagnosis.

Recognition of a recent change of symptoms suggesting early cholecystic neoplasm, in a patient with known gallbladder disease, provides the best chance for effective cholecystectomy. Particular inquiry should be made regarding recent biliary colic, change in frequency and duration of pain, and the onset of weight loss. Should these symptoms be recognized within the first months after onset, instead of at three and one-half months, cholecystectomies might result in a higher percentage of cures.

An additional diagnostic measure is peritoneoscopy, but no details regarding observations have been noted in the literature. This procedure was used in four of our cases, and enabled correct gross diagnosis in two patients. In the other two patients, biliary cirrhosis was diagnosed in one, and the examination was inconclusive in the other. This simple procedure may enable a diagnosis to be made in those advanced cases in which an exploratory laparotomy might hasten the patient's demise.

TABLE IV.—*Malignant Spread of the Tumor.*

Site	Metastases	By Direct Invasion
Liver	10	6
Omentum	8	1
Ducts (biliary)	6	9
Pancreas	6	1
Peritoneum	5	1
Transverse colon	2	0
Portal vein	1	2
Adrenal	2	0
Skin of thigh	1	0
Duodenum	1	1
Stomach	0	1

It might prove profitable to use more liver function tests in evaluating the status of possible cholecystic cancer. Liver function tests showing severe hepatic damage should suggest that the carcinoma is inoperable, and save the patient the necessity of an unsuccessful exploratory procedure.

7. Pathology. All of the 29 patients in this series had some operative procedure. In addition, three patients were examined at autopsy. In our series

TABLE V.—*Operative Procedures.*

Operation	Number of Cases
Exploration	10
Cholecystectomy	7
Cholecystostomy	7
Peritoneoscopy	2
Choledochostomy	1
Biopsy of skin metastases	1
Exteriorization of the gallbladder	1

grossly one case presented the papillary type of tumor, while all others were scirrhous or infiltrative. Microscopically, adenocarcinoma with columnar or cuboidal epithelium was present in 27 cases. The rare squamous cell carcinoma, which has a tendency to form a hard, localized, rapidly metastasizing tumor, was found in two cases. In one of these the gallbladder had perforated, and in the other a cholecystectomy had been performed with recurrence one month later at the ampulla of Vater.

Metastases or direct extension of the tumor occurred in all the cases in our series. These are tabulated in Table IV.

Nineteen of 22 patients had gallstones associated with the carcinoma. In seven patients the gallbladder was not opened and stones were not palpated at

operation. It has been adequately established[5] that cholelithiasis is associated with cholecystic neoplasm.

8. Surgery. Surgery for this condition is unsatisfactory, and seldom results in cure. None of the cases in this series had a five-year cure. The operative procedures that were performed in our series are tabulated in Table V. It will be noted that cholecystectomy was possible in only seven of the 29 cases. Surgery for carcinoma of the gallbladder would seem to have little to offer the patient who has had symptoms of this condition for as long as three months.

SUMMARY

Carcinoma of the gallbladder is an uncommon disease. At the Cleveland Clinic there have been 29 cases of carcinoma of the gallbladder among 350,000 new patients. In the same length of time 1488 cholecystectomies have been done, giving an incidence of 1.9 per cent carcinoma of the gallbladder in the cholecystectomies performed. A diagnosis of cholelithiasis was made in 4459 patients. The percentage of patients with carcinoma of the gallbladder among those having cholelithiasis as determined by roentgen-ray examination was 0.66. The sex ratio in 29 patients was four women to one man; 21 of the 29 cases occurred in patients over 60 years of age.

A history of pre-existing biliary colic was obtained in 17 patients. The earliest symptom was loss of weight, which was present in 23 cases. Pain was present in 21 patients. Nausea or vomiting and jaundice, the last symptom to appear, were present in 16 cases. The liver was enlarged in 22 patients, and there was a palpable mass in 17.

Laboratory findings did not help in the diagnosis of this condition. Only one patient had an appreciable anemia. Liver function tests may be of value in determining the operability of patients with this condition.

Roentgen-ray findings are nondiagnostic, cholecystograms showing only a non-filling gallbladder. Five patients had evidence of extrinsic pressure on other organs.

Peritoneoscopy was of help in the diagnosis of two patients and saved them from the necessity of an exploratory operation.

Adenocarcinoma was present in 27 cases, and squamous cell carcinoma in two patients. All cases had evidence of extension of the tumor or metastases at the time of operation.

Surgery for this condition is unsatisfactory. There were no five-year cures, and cholecystectomy was possible in only seven patients.

CONCLUSIONS

We believe that the incidence of carcinoma of the gallbladder is too low to warrant routine cholecystectomy as a prophylactic measure in all patients with gallstones. Furthermore, the operative mortality from cholecystectomy as a purely preventive procedure would probably at least equal the number of patients who would be expected to develop carcinoma of the gallbladder in later years.

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EXPERIMENTAL RENAL HYPERTENSION AND ITS COURSE FOLLOWING THE PRODUCTION OF A PERIPHERAL ARTERIOVENOUS FISTULA*

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LABORATORY AND CLINICAL STUDIES have indicated that the elevation of blood pressure observed in essential hypertension is the result of increased peripheral resistance.[1] Since this effect is associated with vasoconstriction of the arteriolar beds, at least in the earlier phases, the usual surgical attack on essential hypertension has been an attempt to reduce peripheral resistance by thoracic and lumbar sympathectomy, with splanchnicectomy. The marked reduction of vasomotor tone of large portions of the tissues of the legs and splanchnic regions has failed, however, to lower arterial pressure in many patients in carefully selected groups.[2-6]

The pronounced loss of peripheral resistance occasioned by a peripheral arteriovenous fistula has been shown repeatedly to result in a significant fall in arterial pressure, especially in the diastolic pressure.[7-10] It was of interest to us in 1944, while studying dogs with femoral arteriovenous fistulas, to observe the actual effects of a fistula on the course of experimentally induced renal hypertension.

METHODS

Twenty-seven adult mongrel dogs of medium size were used. Observations were made of the arterial blood pressure and pulse rate with the aid of the Hamilton manometer.[11] Serial roentgenograms of the thorax in the supine anteroposterior position was made during inspiration at a distance of one meter to permit measurement of the cardiac silhouette by planimeter. Electrocardiograms were made employing the three standard leads and the Wolferth lead IV. Circulating blood volume was measured by photo-electric determinations of the blue dye, T1824, in the plasma of single five-minute blood samples.[12, 13] Circulation time from the saphenous vein to the carotid sinus was easily measured by noting the occurrence of hyperpnea which resulted from the intravenous injection of 1.5 mg. of sodium cyanide in 1 cc. of normal saline solution.[14] Blood urea was determined by the aeration method of Van Slyke and Cullen,[15] using boric acid solution in collecting tubes.[16] Hematocrit

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and hemoglobin determinations were also made every one to two weeks during the nine months following the operative procedures next described.

To produce chronic hypertension, the kidney was exposed by flank incision and wrapped in a square of silk cloth. Ether anesthesia and sterile technic were used. In three dogs, permeable cellophane was used instead of silk, as described by Page.[17, 18] The second kidney was similarly wrapped one week later.

Eight dogs, including the three with cellophane-wrapped kidneys, were used for a control study of hypertension alone. In the other 19, arteriovenous fistulas were produced after chronic hypertension had developed. Necropsy was performed on all animals and both gross and microscopic studies were done.

GENERAL OBSERVATIONS ON THE PRODUCTION OF RENAL HYPERTENSION

Elevated arterial blood pressure usually developed three or four weeks after the operation on the second kidney. Coincidentally, there was noted a change in behavior in many of the animals. Certain animals became apathetic and developed a rapidly fatal malignant hypertension. Although such a condition occurred in six weeks in two instances, it was generally noted ten to 14 weeks after the second operation, and was initiated by vomiting, bloody diarrhea and dyspnea. In other hypertensives, there was a definite increase in nervousness and irritability which persisted throughout the period of observation. This has been observed clinically.

In seven instances a sinus tract from the involved kidney to a subcutaneous abscess in the flank developed. This was the only postoperative complication, and it resolved in all but two instances, in which minute chronic sinuses persisted.

Arterial pressure measured directly in the femoral artery of the unanesthetized trained dogs gave control pressures that varied from 185 systolic and 90 diastolic to 240 systolic and 110 diastolic, expressed in millimeters of mercury, with a mean of 200 systolic and 100 diastolic. About four weeks after the second operation a significant rise in systolic and diastolic pressures was noted. A maximum was reached in eight to ten weeks, representing a range of 270 systolic and 165 diastolic to 305 systolic and 220 diastolic. This effect was observed in all but two dogs, and in these infection delayed the second renal operation for several weeks. At necropsy, marked hypertrophy of the second kidney was noted in these two animals. Malignant hypertension, appearing in from four to 12 weeks, resulted in death, while in those dogs surviving, there was a gradual decline in arterial pressure, of about 30 mm. of mercury, commencing after the twelfth week and continuing during subsequent months.

The pulse rate was obtained by palpation and by the Hamilton manometer. A sustained significant rise in rate appeared during the period in which hypertension developed. Preoperative rates of 70 to 80 beats per minute at rest increased to rates of 110 to 150 with a simultaneous change from sinus arrhythmia to sinus tachycardia.

Planimetric measurement of the cardiac silhouette revealed no significant increase while hypertension was increasing to maximal levels (Fig. 1). Subse-

quently, a very gradual increase was observed during sustained hypertension. In three dogs killed at 32 weeks, an increase of 27 per cent had occurred (Fig. 1). At necropsy, cardiac dilatation as well as hypertrophy of the myocardium was found.

Electrocardiograms, taken weekly during 32 weeks after the second operation, showed no constant significant alterations, except the change in rhythm

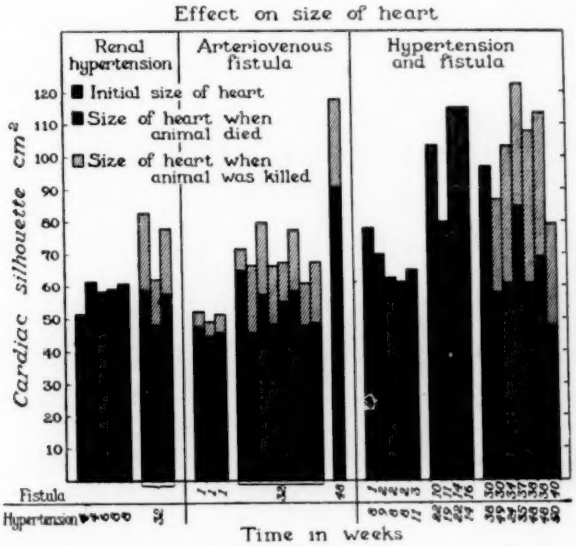

FIG. 1.—Graphic representation of cardiac size of typical animals at various intervals in square centimeters, as determined by planimeter from roentgenographic silhouette. Groups having only renal hypertension, only arteriovenous fistula or a combination of both are compared. The baseline records the total duration in weeks of the fistula or hypertension. The variation in initial cardiac size showed a correlation to body weight, whereas the subsequent degree of enlargement did not.

with the development of tachycardia. In the later records, there was some suggestion that the T_3 waves were inverted more frequently. Slight depression of the ST segment in lead II, and slight elevation in lead III occurred also. No change in axis deviation was observed. However, great variability of the electrocardiogram of normal dogs exists generally.[19]

Circulation time was measured by noting the time of onset of hyperpnea after the injection of sodium cyanide into the right saphenous vein. Normal limits were between seven and nine and a half seconds for this group. There was a slight decrease in circulation time during the period of maximal hypertension amounting to about one second. In two of three dogs observed for 32 weeks, the circulation time increased one to three seconds over control values. In dogs which developed cardiorespiratory symptoms from malignant hyper-

tension, the circulation time was prolonged four to ten seconds, probably on the basis of cardiac failure.

The control blood volume was 76 to 90 cc. of whole blood per kilogram of body weight. No significant increase was noted over 32 weeks of observation (Fig. 2).

Preoperative determinations of blood urea gave values that ranged from 20 to 31 mg. per 100 cc. While occasional rises to 50 mg. were observed during

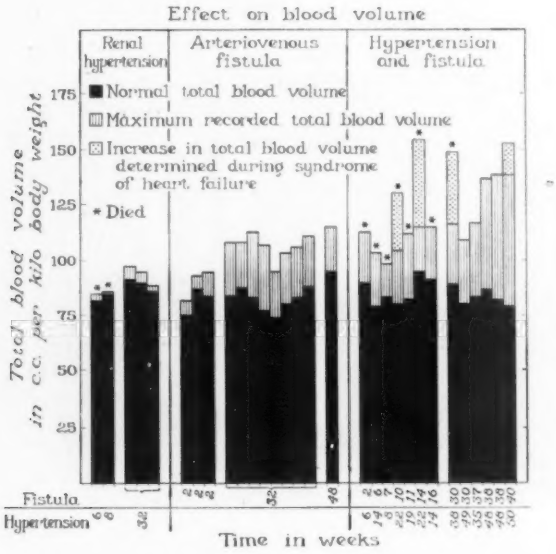

FIG. 2.—Graphic representation of total circulating blood volume as determined by the use of the azo dye, T1824, at various intervals. Groups having only renal hypertension, only arteriovenous fistula or a combination of both, are compared. The baseline records the total duration in weeks of the fistula or hypertension. Note the close agreement of initial values despite variations in total body weight.

the postoperative period, all values were within normal limits, except those of the dogs dying of the malignant phase whose terminal value for blood urea was between 185 and 214 mg.

Hematocrit and hemoglobin determinations showed a slight decrease postoperatively for several weeks, as did body weight, but thereafter were within normal limits. Two dogs dying of the malignant phase of hypertension had hemoconcentration, probably on the basis of dehydration. Pathologic retinal changes were noted with the ophthalmoscope in certain hypertensive dogs. In the 27 animals with hypertension, retinal detachments were noted. Two occurred in the control group of eight hypertensive dogs, and subsequently these two animals died from malignant hypertension. In the other group of

hypertensive animals, three of the retinal detachments occurred three to five weeks after the femoral arteriovenous fistula had been produced. The detachments, seven of which were bilateral, occurred from three to 14 weeks after the second renal operation and involved 25 to 75 per cent of the retina. Arteriovenous nicking and flame-shaped hemorrhages were observed shortly before detachment. Some retinas later showed regression in the extent of detachment.

In a few of the dogs a rounded area of opacity in the optic lens appeared, beginning as small stellate shadows near or at the midpoint of the anterior surface of the lens, and measured 4 to 8 mm. in diameter in a few days, appearing white by reflected light and black to transmitted light. Bilateral opacities were found in two dogs, and occurred with retinal detachment in one instance. In one dog they resolved after a few weeks. Microscopic examination of the eyes after necropsy failed to reveal structural changes of significance.

Of the eight dogs with hypertension alone, two died of the direct effects of malignant hypertension and three died of hemorrhage from the renal pedicle. The three dogs whose kidneys were wrapped in cellophane were killed after 32 weeks.

At necropsy, all of the dogs had marked pallor of the mucous membranes. In the two dogs dying of malignant hypertension, 10 to 15 cc. and 25 to 30 cc., respectively, of serosanguineous pericardial fluid was present. One of the latter dogs had 2200 cc. of sanguineous ascitic fluid that contained 185 mg. of urea per 100 cc.

The lungs of the two dogs dying of the malignant phase of hypertension were firm and congested. Sections through the bronchi revealed much serosanguineous frothy exudate. Microscopically, there was marked capillary congestion and a decrease in alveolar air space, which was the site of hemorrhagic edema. In some areas, polymorphonuclear leukocytes were present, probably representing a secondary bronchopneumonic process. The lungs of the other animals were essentially normal.

In the dogs with kidneys wrapped in silk, the ratio of heart weight to body weight was as great as 0.013. If 0.0086 is the maximal normal ratio, as indicated by the results of a previous study of a large group of normal dogs in this laboratory, it is evident that moderate hypertrophy had occurred, involving both ventricles. By contrast, the hearts of the three dogs whose kidneys were wrapped with cellophane showed little hypertrophy, even though they were observed for a longer period.

Fibrous adhesions occurred among the abdominal organs, with a greater reaction resulting from the use of silk. The kidneys were removed, along with an investing fibrous shell which measured 3 to 5 mm. in thickness. A purulent zone was often found between the silk cloth and the outer fibrous shell in the specimens wrapped with silk cloth, but was not noted in those wrapped in cellophane. The fibrosed renal capsule measured 5 mm. in thickness in the specimens wrapped in silk, while in those wrapped in cellophane the zone of fibrous reaction measured no more than 2.5 mm. in thickness. Sections of the specimens revealed patchy areas of hemorrhage and wedge-shaped segments of

softening of the cortex representing focal infarction and necrosis (Fig. 3). Microscopically, there were moderate to severe pathologic changes in all specimens, being more marked in those which had been wrapped in silk. The renal parenchyma contained areas, varying in size, of cortical necrosis and interstitial hemorrhage extending along the pyramids and originating from the vessels of the infarcted area. The small arteries and arterioles had moderate to marked sclerosis of the media, with a correspondingly decreased ratio of lumen to wall; a ratio of 1:1 was not uncommon. Occasional hyalinized glomeruli were observed.

FIG. 3.—Mounted section of a kidney nine months after being wrapped in silk cloth (not shown). The fibrosed capsule measured 4 mm. in thickness. Dark areas of hemorrhagic necrosis are shown in the parenchyma (Mallory-Heidenhain stain x1.2).

The liver in the animals dying of the malignant phase showed passive venous congestion. The spleen, other than for fibrous adhesions of the capsule, appeared normal except in those animals killed with pentobarbital sodium. This drug caused congestion and enlargement. The mesenteric lymph nodes were enlarged, and microscopically showed nonspecific low-grade inflammation.

Microscopic examination of blocks of tissue removed from the web between the right second and third toes revealed arteriolar changes consistent with those of clinical essential hypertension.

Comment. The efficacy of the technic of Page in producing a chronic arterial hypertension by renal perinephritis[17, 18] was amply demonstrated in this group of dogs. In all but two of the 27 animals in which this technic was used, a significant and sustained elevation of arterial blood pressure was observed. The two failures might be explained by the compensatory hypertrophy of one kidney which occurred in the four weeks between stages necessitated because of infection following the first stage. The time of appearance, severity, duration, and pathologic effects of the renal hypertension were in agreement with the observations of Graef and Page.[20] We noted a more severe effect when silk cloth had been used, with a greater incidence of the malignant phase of hypertension resulting, than with the use of cellophane. Marked fibrosis about the renal pedicle may explain this effect, in part. The retinal detachment, which occurred in 30 per cent of the dogs, has been previously described,[21, 22] but we found no reference to the peculiar lenticular opacities. In general, the clinical course and pathologic findings closely paralleled those observed in patients with benign and malignant essential hypertension.[23, 24]

THE EFFECTS OF A PERIPHERAL ARETERIOVENOUS FISTULA ON THE COURSE OF CHRONIC RENAL HYPERTENSION

A group of 19 dogs, in which arterial hypertension had been produced by wrapping the kidneys in silk, was used to study the effects of a femoral arteriovenous fistula. A median of eight weeks (range six to 16 weeks) elapsed after the kidney had been wrapped in silk cloth. The median pressure obtained for the group immediately before producing the arteriovenous fistula was 270 systolic and 160 diastolic as compared with the median control value of 200 systolic and 100 diastolic. A few of the dogs had systolic pressures of 305 as obtained in the femoral artery with the Hamilton manometer.

The dogs were anesthetized with intravenously administered pentobarbital sodium and a side-to-side femoral arteriovenous fistula was made. The technic used for the suture anastomosis has been reported previously.[25] The dogs had a median body weight of 11 Kg. (range 6.8 to 16.2 Kg.), and the median length of the fistula at the completion of the operation was 2 cm. (range 1.6 to 3.7 cm.). Determinations of arterial pressure were made within 24 hours of operation, daily for a week, and weekly thereafter. The laboratory observations described in the previous section were repeated at least every week.

Results. Immediately after the production of the fistula, the arterial pressure fell appreciably, the median value being 230 systolic and 12[illegible] diastolic as compared to 270 and 160, respectively, before operation (Table I). The fall in pressure varied greatly among the animals. In those with mild hypertension, the postoperative value generally approximated the normal pressure for that dog, but in three of these the pressure fell below the normal value.

Although a significant fall in both the systolic and diastolic pressures occurred after the production of a fistula, recovery of these pressures to hypertensive levels was rapid. In some instances, the systolic pressure attained, within ten days, the level noted before the production of the fistula. It was interesting, however, that although the systolic pressure at the time of death was higher than that observed before production of the fistula in about half of this group, the diastolic pressure was higher in only about a fourth of the group. This was evidence that the fistula had affected the diastolic pressure more profoundly than the systolic as a result of the loss of peripheral resistance. Nevertheless, the fact that the arterial pressures readily returned to severe hypertensive levels in spite of a large arteriovenous fistula indicates the predominant role played by widespread arteriolar constriction in influencing the systemic arterial pressure of these dogs.

Nine dogs died within six weeks after the production of the fistula (47 per cent). Of these, four died as a result of hemorrhage from the site of the anastomosis one or two weeks after operation (dogs 2, 5, 16 and 18). In that short time, the arterial pressure had risen significantly above the level noted postoperatively. Of the other five animals, two died of uremia and renal insufficiency (dogs 8 and 11); the value for blood urea was 188 and 202 mg. per 100 cc., respectively, at the time of death. Both dogs had retinal detachments and a short terminal course characterized by vomiting and bloody diarrhea. In

one, marked jaundice developed during the last two days of life. Two dogs died of cardiac failure with terminal edema and severe dyspnea (dogs 4 and 13). One animal died of hemorrhage following arterial puncture performed in the determination of blood pressure (dog 12).

Four dogs (21 per cent) of the group of 19 died between ten and 14 weeks after the production of the fistula. In these animals a severe dyspnea of sudden

TABLE I.—*Data on Dogs With Renal Hypertension and Arteriovenous Fistula.*

Dog	Weight, Kg.	Normal Blood Pressure mm. of Mercury	Weeks Since Renal Opera-tions	Blood Pressure Before and After Arteriovenous Fistula Was Made			Arteriovenous Fistula Duration at Death, Weeks	Arteriovenous Fistula Length, cm.	Cause of Death	Estimated Increase of Heart Weight, Per Cent
				Before	Immediately After	Later				
1	8.5	200/105	15	280/170	230/125	300/175	34	2.5	Killed	31.5
2	12.0	205/90	9	270/160	200/100	235/130	1	2.0	Hemorrhage	31.0
3	9.8	207/95	16	265/150	230/120	270/155	10	3.5	Cardiac	63.3
4	6.8	210/120	8	300/205	240/140	255/135	3	1.6	Cardiac	
5	11.0	190/95	7	280/175	240/125	250/130	2	1.7	Hemorrhage	31.6
6	11.3	200/105	8	280/155	245/135	265/135	11	2.0	Cardiac	76.2
7*	14.2	200/100	9	240/125	190/95	265/155†	14	3.7	Cardiac	71.5
8	10.0	210/115	8	300/160	240/125	275/150	4	2.0	Cardiac and renal	128.0
9	8.0	215/120	7	305/220	285/155	310/170	14	1.8	Cardiac	70.0
10	14.3	160/80	9	225/130	190/105	225/120	30	2.7	Renal	59.5
11	16.2	195/110	7	250/135	230/110	280/155	6	2.7	Renal	67.4
12	10.0	200/100	7	285/190	240/145	260/155	2	3.0	Hemorrhage	
13	14.6	175/95	8	230/140	165/80	205/110	1	2.0	Cardiac	
14	9.2	230/120	10	305/190	240/125	305/195	40	2.0	Killed	35.7
15	10.6	195/90	13	250/140	200/100	310/175	35	2.0	Killed	30.2
16	8.7	210/100	6	285/190	240/150	290/160	2	1.6	Hemorrhage	30.6
17	12.8	215/105	10	250/145	200/90	250/130	38	2.5	Killed	45.5
18	11.5	180/105	7	265/160	225/130	230/135	1	2.5	Hemorrhage	25.5
19	16.2	185/90	11	260/155	210/115	300/165	38	2.5	Killed	30.5
Median	11.0	200/100	8	270/160	230/125	265/155	10	2.0		
High	16.2	230/120	16	305/220	285/155	310/195	40	3.7		
Low	6.8	160/80	6	235/125	165/80	205/110	1	1.6		

* Four weeks elapsed between renal operations.

† Terminal recording.

onset developed, which lasted but two or three days before death occurred (dogs 3, 6, 7 and 9). Two of these four dogs had bloody diarrhea, vomiting and an elevated value for blood urea at the time of death.

The remaining six dogs (32 per cent) of the group of 19 survived more than 30 weeks after the production of the fistula. Five (dogs 1, 14, 15, 17 and 19) of these were killed between the thirty-fourth and fortieth weeks. Except for one (dog 14), they had a relatively uneventful course in spite of severe hypertension. In one dog (dog 14) marked dyspnea developed 30 weeks after the fistula had been produced. Studies at that time revealed pronounced cardiac enlargement, pulmonary congestion, and decidedly increased circulation time and blood volume. After phlebotomy and withdrawal of 150 cc. of blood, followed by the intravenous injection of 20 cc. of 50 per cent solution of dextrose, the animal made a rapid recovery and had an uneventful course until it was

killed ten weeks later. The blood volume of this dog during the period of cardiac failure was 152 cc. per kilogram of body weight, and subsequently it decreased to 137 cc. which was maintained until the time of death a few months later (Fig. 2).

One dog of this final group of six animals died under observation, apparently as the result of renal failure.

The laboratory findings in this series of 19 dogs were remarkable in that more pronounced physiologic and pathologic changes were noted in them, especially in regard to cardiac size and blood volume, than in either those animals with hypertension alone or in another group of 23 dogs with arteriovenous fistula alone which was studied similarly in this laboratory (Figs. 1 and 2).

In animals having hypertension and fistula, cardiac enlargement noted one to three weeks after the production of the fistula was much greater than that observed with hypertension or fistula alone of comparable duration. Enlargement observed ten to 16 weeks after the production of a fistula in hypertensive dogs was comparable to the maximum seen in dogs with fistula alone of 32 weeks' duration (Fig. 1).

The blood volume of the hypertensive animals did not increase significantly until the fistula was produced, and then a rapid increase was observed. Determinations revealed that in the hypertensive dog, the blood volume may increase, in the two weeks following production of the fistula, to the degree observed in dogs with a fistula alone of 32 to 48 weeks' duration. The augmentation was a slow process except for the late rapid increase in blood volume, associated with cardiac failure. In the majority of hypertensive animals surviving 30 weeks or more after the production of the fistula, the blood volume was much greater than in a corresponding group with fistula alone. This increase was exclusive of that observed during a period of cardiac decompensation (Fig. 2).

The values for blood urea in this group of 19 dogs were within normal limits, except for four dogs which exhibited vomiting and bloody diarrhea terminally. The blood urea of these animals rose rapidly to levels above 185 mg. per 100 cc.

Circulation time was studied in the entire group; a gradual increase was observed about four weeks from the time the fistula was produced. This increase amounted to three to five seconds, except in the six dogs which died of cardiac failure. During the time that those animals exhibited marked dyspnea, increases in circulation time to the extent 15 to 40 seconds above the normal values were observed and were accompanied by a rapid increase in cardiac size and blood volume.

Electrocardiograms revealed a persistence of the tachycardia which developed in step with the hypertension. In those animals with cardiac failure, varying degrees of arrhythmia were noted. The records of those dogs surviving more than 30 weeks after the production of a fistula revealed decreased voltage in all leads and minor alterations of the complexes which were considered of doubtful significance.

The hematocrit and hemoglobin determinations, which had decreased slightly during the period following the operations on the kidneys, fell still lower after the production of the arteriovenous fistula. This was due to the marked hemodilution which occurred rapidly after the fistula was made, rather than to any blood loss at operation. The early increase in blood volume was due primarily to a decided rise in plasma volume. Return of the hematocrit and hemoglobin determinations to normal was not observed in this group of dogs.

Necropsy Findings. An analysis of this series of animals revealed that five of the 19 dogs died of hemorrhage. Of the remaining 14 dogs, six (43 per cent) died of cardiac failure and three (21 per cent) succumbed to renal insufficiency and uremia. Consequently, 64 per cent died of the combined effects of renal hypertension and arteriovenous fistula. Five dogs, or 36 per cent, survived and were killed between 34 and 40 weeks after the production of the fistula. Four of the five were killed by using pentobarbital sodium, and one with ether; exsanguination was carried out in all five.

At necropsy, the mucous membranes were pale in all the animals. One dog dying of renal failure had intense jaundice (dog 8). The animals succumbing to renal failure and uremia had evidence of vomiting and bloody diarrhea. The dogs dying of cardiac failure had frothy serosanguineous effusion about the nares and mouth. All 19 of the dogs had dilated superficial veins in the leg with the fistula, and all but two had from moderate to marked edema of that leg. Retinal detachments were observed in six of the 19 dogs. These occurred before the fistula had been produced in three (dogs 4, 12 and 18), and after the production of the fistula in three (dogs 8, 11 and 16). The pathologic findings in these eyes have been described in the previous section. About 20 cc. of free serosanguineous fluid was found in both pleural spaces in two dogs with cardiac symptoms.

1. Lungs. In the seven dogs dying with signs of cardiac failure, the lungs were firm and congested. The cut surface revealed marked serosanguineous effusion in the bronchi and parenchyma. Microscopically, there was much venous congestion and thickening of the alveolar walls. The alveoli were decreased in size and they were the site of hemorrhagic edema. There was patchy bronchopneumonia in several instances. The lungs of the remaining 12 dogs were essentially normal grossly, but venous congestion was present microscopically. In addition, serous exudate was noted in the alveoli of three dogs (dogs 11, 14 and 18).

2. Heart. The weights ranged from 90 to 202 Gm. in 16 instances in which the weights were recorded. The computed normal weights for the hearts of the 16 dogs ranged from 64 to 134 Gm., employing 0.0086 as the ratio of heart weight to body weight. This estimated increase in heart weight agreed with the evidence of dilatation and hypertrophy observed in the cardiac roentgenographic silhouette.

Grossly, the hearts were moderately to markedly dilated, with definite muscular hypertrophy of the walls of both ventricles. In the dogs dying of cardiac

and renal failure, there were areas of petechial hemorrhage beneath the epicardium and endocardium. In some of the greatly dilated hearts, the tricuspid valves appeared incompetent. Microscopically, there was pronounced venous and capillary congestion. In three, there were patchy areas of scarring in the myocardium. In one heart, there was an area of fresh infarction and suppurative myocarditis (dog 3). The muscle fibers of those hearts were hypertrophied, and in some instances there was interstitial edema.

On abdominal examination two dogs had 25 to 50 cc. of free serosanguineous fluid. The organs and mesentery were adherent as a result of the great fibrosis about the kidneys.

3. Liver. In the ten animals in which the fistula had been present for more than ten weeks, the liver was congested and enlarged. Microscopically, there was much congestion of the central veins and adjacent sinuses, with atrophy of the hepatic cells. In one dog, the veins of the portal radicles also were greatly congested, and the adjacent hepatic cells were atrophied (dog 10). This dog and one other (dog 3) had suppurative hepatitis with areas of hemorrhage.

4. Kidneys. These organs were encased in a thick fibrous shell, and in many instances a purulent exudate was found between this shell and the silk cloth covering the kidney. The renal capsule was fibrosed and was from 2.5 to 5 mm. in thickness. In four dogs, the right kidney was found to be almost entirely destroyed by hemorrhagic infarction and necrosis. Strangely enough, none of these animals had apparent renal failure (dogs 1, 9, 13 and 16). Of the remaining dogs, the left kidney was hypertrophied in about 60 per cent, the difference in weight being 4 to 10 Gm. Decided pathologic changes were observed microscopically. Among these were extensive round-cell infiltration, tubular dilatation and atrophy, venous congestion, arteriolar hypertrophy and occasional glomerular hyalinization. Patchy areas of cortical necrosis and fibrosis were common (Fig. 3). In the more severely damaged kidneys, extensive hemorrhagic infarction and necrosis were the major findings.

5. Spleen. This organ was relatively normal in size (24 to 37 Gm.) unless an anesthetic agent was used terminally. Microscopically, in seven instances a decrease in lymphoid elements of the follicles, associated with central and peripheral fibrosis of the follicles, was noted. These microscopic changes had been observed in some of the dogs with fistulas alone which were of long duration.

6. Extremities. Edema of the limb bearing the fistula was more widespread and more frequent in hypertensive dogs than in otherwise normal dogs. Blocks of tissue were cut from between the second and third toes of both feet. Microscopic examination revealed great dilatation and apparent thinning of the walls of the arterioles in the foot on the side with the fistula. An increase in fibrous tissue was also observed (Fig. 4a). The arterioles in the opposite foot had extensive hypertrophy of the media and intimal proliferation. The ratio of the diameter of the lumen to the arteriolar wall was 1:1 in many instances (Fig. 4b).

Comment. The number of reported clinical cases of arteriovenous fistula in which there was an associated arterial hypertension appears to be very small.[26, 27] This seems unusual in view of the fact that hypertension may cause more than 350,000 deaths yearly in the United States, or almost twice those caused by cancer.[28] This posed the question of whether a fistula might effectively reduce the peripheral resistance sufficiently to mask an essential hypertension. The probability that a fistula might not exert a favorable clinical influence on hypertension in view of the marked cardiovascular disturbances resulting from either lesion was evident before this study was undertaken; however, actual proof was obtained from these experimental observations.

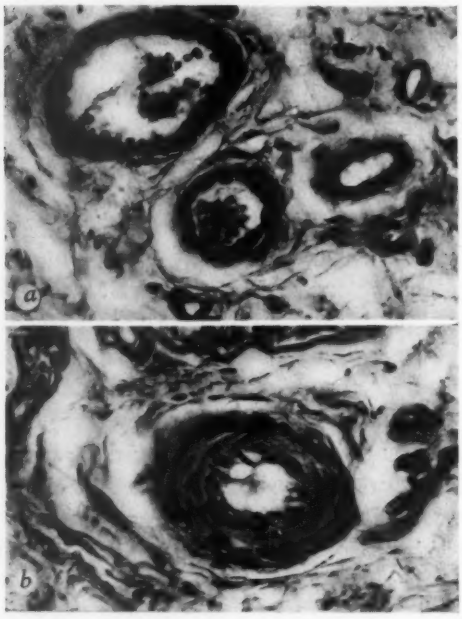

FIG. 4.—(a) Arterioles of the left foot. This dog had severe hypertension and a chronic left femoral arteriovenous fistula. Note the marked dilatation and thinned walls of these vessels (hematoxylin and eosin x270). (b) A comparable arteriole from the right foot of the same animal. The intimal proliferation and medial hypertrophy are in contrast to the findings in the arterioles from the side with the fistula. The femoral arterial pressure was 310 systolic and 175 diastolic (hematoxylin and eosin x270).

It became readily evident from the clinical course of these dogs that the physiologic changes resulting from a fistula were even more profound and detrimental in the presence of renal hypertension than was either hypertension or fistula alone. The studies of blood volume and cardiac size demonstrated a definite and early increase following the production of the fistula. Furthermore, these determinations made when the fistula had been present for more than 30 weeks revealed a large increase over the values noted in dogs with either a fistula or renal hypertension alone of corresponding duration (Table II).

At necropsy, the pathologic alterations in the organs were much more severe, grossly and microscopically, in the group with both hypertension and fistula than in those with either condition alone. A comparison of the estimated increase in the weight of the heart made in the various groups after 32 weeks, the same method being employed in all cases, disclosed percentage increases as follows: arteriovenous fistula, 20; renal hypertension, 25; and both hypertension and fistula, 45.

A comparison of mortality rates indicates further the disastrous effect of the combination of arteriovenous fistula and hypertension. Considering only

those dogs dying directly as a result of the lesion produced, one notes a significant rise in mortality in the group with a combination of hypertension and a fistula. The mortality percentages for dogs with the various conditions were as follows: arteriovenous fistula, 0; renal hypertension, 25; and both hypertension and fistula, 64.

Consequently, on the basis of these experimental studies, it would appear that the production of an arteriovenous fistula has no place in the surgical treatment of arterial hypertension.

TABLE II.—*Changes in Blood Volume and Cardiac Area of Dogs With Stated Conditions after 32 Weeks*

Condition	Average Increase, Per Cent	
	Blood Volume	Cardiac Area
Arteriovenous fistula	31	34
Renal hypertension	5	31
Hypertension and fistula	57	63

SUMMARY AND CONCLUSIONS

Sustained severe, chronic arterial hypertension was successfully induced in all but two of the 27 dogs by means of the Page technic. The renal hypertension, developing about four weeks after wrapping the kidneys in silk cloth or cellophane, reached levels of 305 systolic and 220 diastolic, expressed in millimeters of mercury. Many widespread pathologic changes were noted at necropsy. Transition into a fatal malignant phase occurred in several instances.

In a series of 19 hypertensive dogs, lateral femoral arteriovenous fistulas were produced in order to determine their influence on the course of the renal hypertension. On the basis of the evidence obtained, the following conclusions are drawn:

1. The arterial pressure observed in experimental renal hypertension in dogs was not permanently lowered by an arteriovenous fistula of the femoral vessels.

2. Cardiovascular alterations of a greater magnitude occurred as a result of combining renal hypertension and fistula than from either lesion alone.

3. The mortality was greater and the pathologic changes, both gross and microscopic, were more widespread and severe in the group of dogs with both renal hypertension and fistula than in the groups with either renal hypertension or fistula alone.

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INTRAVENOUS PROCAINE INFUSIONS IN THE POSTOPERATIVE PERIOD*

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INTRAVENOUS ANESTHETICS have been used for a variety of conditions, but their effectiveness as postoperative analgesics has not been widely tested. Because of the recognized inhibitory effect of pain upon recovery, as well as the vicious circle produced by pain on the vasoconstrictor and hypertonic muscle reactions, it seemed advisable to test intravenous procaine for its postoperative analgesic usefulness.

Bier,[3] in 1908, was the first to use local anesthetics intravenously, and he produced complete analgesia of the limb. With a tourniquet around a limb, he injected the anesthetic into a vein peripheral to the tourniquet, producing a local anesthetizing effect. In 1937 Lewy treated buzzing of the ears with intravenous local anesthetics.[7] Procaine was employed at the Mayo Clinic[8] in 1940 for the treatment of pruritis resulting from jaundice, and by Dos Ghali[4] in 1941 for the treatment of asthmatic dyspnea, coronary spasm, coma, hypertension, anuresis, hemoptysis and postoperative embolism.

Gordon,[6] in 1943, anesthetized serious burn injuries by means of intravenous procaine. He used 200 to 500 cc. of a 0.1 to 0.2 per cent solution in physiologic saline, or in 5 per cent glucose solution. The infusion took two hours and contained a total of 1 Gm. of procaine. Analgesia appeared ten minutes after starting the infusion and had an effective duration of 12 to 16 hours.

In 1945 McLachlin[9] reported administering procaine intravenously after gastrectomies, cholecystectomies, lobectomies and herniotomies. He employed procaine in the form of an intravenous infusion containing 1 Gm. in 500 cc. salt solution administered over a period of one to one and a half hours. In the same year Ameuille[1] confirmed Dos Ghali's good results with intravenous procaine therapy. He injected 20 cc. of a 1 per cent procaine solution three times a week in the treatment of bronchial asthma over a period of many weeks, and reported eventual recovery. Favorable results were also obtained in the following conditions: pneumonic embolism, angina pectoris, acute edema of the lungs, chronic dyspnea, vasomotor rhinitis, anuria and pruritis caused by jaundice. Durieu[5] in 1946 confirmed earlier good results with procaine infusions in the treatment of bronchial asthma.

In 1946 State and Wangensteen[10] reported 27 cases of serum poisoning and urticaria treated by intravenous procaine infusions. Among 16 patients suffering from serum poisoning there were only two who did not respond at all to the treatment, ten were quickly cured, and four were temporarily

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improved. Most of these patients had resisted all other methods of treatment. In seven cases of urticaria the attack could always be relieved, but hypersensitivity was not cured. The infusion used contained 1 Gm. of procaine in 500 cc. of physiologic salt solution and was given over a two hour period. In 1946 Appelbaum[2] also successfully used intravenous procaine infusions in cases of serum poisoning following tetanus antitoxin injections.

EXPERIENCE IN POSTOPERATIVE TREATMENT

Intravenous procaine infusions have been given postoperatively in a wide range of surgical patients. Initially, we gave 400 cc. of 0.25 per cent procaine solution, allowing three to four hours for the infusion. As operations were generally done under local anesthesia the infusion was started late in the afternoon of the day of operation. Our apparatus was that used by the American Army in World War II for plasma infusions. Later on a dosimeter was inserted. It was never necessary to cut down on the veins used. With this procedure no unfavorable reactions were encountered, but sometimes the effect was not quite satisfactory. Accordingly, the dose was then concentrated, using a 0.5 per cent solution of procaine in 200 to 250 cc. of physiologic salt solution, given over a period of two to two and a half hours. The maximum procaine injected was 1.25 Gm. Optimal rate of infusion appeared to be 40 to 50 drops per minute.

The infusions were used on 80 patients. In 95 per cent of these, satisfactory analgesia, lasting 10 to 14 hours, was produced. In all but four cases, no other sedation was required throughout the postoperative period. Intravenous procaine proved insufficient to relieve pain following thoracoplasty operations on patients with pulmonary tuberculosis. Probably these patients were already aware of the pleasantly narcotizing effect of morphine. There may have also been psychic factors involved in these patients' need for morphine. There were other patients in the same ward who were receiving morphine at the time, and this probably influenced the postoperative tuberculous patients.

About ten minutes after the start of the infusion the following reactions could usually be observed: Sensation of mild warmth all over, dizziness, slight headache, buzzing of the ears, and sometimes sweating. If the rate of flow were reduced these symptoms disappeared, and after about 15 minutes from the start of the infusion the patient noted analgesia. In only one patient did we observe a more severe reaction, consisting of excessive sweating, dizziness and rapid pulse rate. When the infusion was interrupted these symptoms ceased, and some minutes later the infusion could be continued without discomfort. Camphor, caffein, and ephedrine given simultaneously helped to control these side reactions. In no case did we observe severe signs of intoxication such as coma, spasm, or epileptiform attacks which may occur on overdose of procaine for local anesthesia. During the infusion, blood pressure usually increased, the rise in systolic pressure being 10 to 40 mm. of mercury.

As stated above, even after serious operations no other analgesic drug was required except in 5 per cent of the patients. If an anodyne was required on the following day we injected 10 to 20 cc. of 1 per cent procaine solution slowly, taking four to five minutes to complete the injection. Complete analgesia was thereby achieved.

A great difference was noted in the postoperative condition of patients treated by procaine infusions, as compared to those receiving morphine. The former are more alert, move easily in their beds with free gestures and do not appear to be acutely ill. The latter are obviously stupefied, tired and depressed. As an example I cite the following. One patient, suffering from dysbasia intermittens had had an unsuccessful Doppler operation a few months earlier. On walking 40 to 50 steps he experienced almost intolerable pain in the sural muscles, which rendered him incapable of moving further. This patient was given an intravenous procaine infusion, consisting of 200 cc. of a 0.5 per cent solution, once a day for eight days. Amelioration of the symptoms was observed after each treatment, and after the whole series he was able to walk 600 to 700 steps without pain. The infusions produced almost no side reactions, and after each treatment the patient walked briskly. At the same time there was a patient on the ward who had received 20 mg. of morphine and ½ mg. of atropine as preoperative medication. For some reason the operation was postponed, and the patient lay all day long in bed, appearing pallid, depressed and complaining of weariness. The difference between the effect of the two drugs was striking.

In none of the 80 patients did we encounter respiratory complications or circulatory disturbances, and none of the patients vomited. Thus the most frequent consequences of morphine injections were avoided. Procaine infusions after abdominal operations avoid the constipating effect of morphine, and rapid resumption of intestinal activity takes place. This is probably one reason why patients treated with procaine infusions appear to be in relatively good condition. It is suggested that if mild toxic symptoms occur at the beginning of the infusion, the rate of flow be reduced during the first ten minutes.

SUMMARY

1. Intravenous procaine infusions have been used to produce postoperative analgesia in 80 patients after a wide variety of operations.

2. The maximum amount injected was 1.25 Gm. procaine, given in 250 cc. of 0.5 per cent procaine in physiologic salt solution. The infusions took two to two and a half hours.

3. Satisfactory analgesia was produced in 95 per cent of the patients about 15 minutes after starting the infusion. Analgesia lasted 10 to 14 hours.

4. In four patients with pulmonary tuberculosis who had undergone thoracoplasty, supplementary doses of morphine were required to control pain.

5. In all patients the side reactions were mild, confined to a sensation of warmth, slight dizziness and headache, buzzing of the ears, and sometimes

sweating. These reactions could be controlled by reducing the rate of flow of the infusion.

TABLE I.—*Summary of Clinical Data.*

Operations	Number of Cases		Result		
	Male	Female	Good	Medium*	Ineffectual
Crural amputations	1	1	2		
Femoral amputations	..	2	1	1	
Appendectomies	3	2	5		
Ileotransverse resection of colon for carcinoma	1	1	1	1	
Resection of colon for carcinoma	1	2	2	1	
Abdominosacral extirpation of rectum for carcinoma	1	1	1	1	
Kraschke operation for carcinoma of rectum	1	..	1		
Radical mastectomies	3	..	2	1	
Cholecystectomies	5	1	4	2	
Femoral herniorrhaphies	..	2	2		
Inguinal herniorrhaphies	2	3	5		
Abdominal herniorrhaphies	1	3	3	1	
Exploratory laparotomies	5	3	8		
Lobectomy	1	..	1		
Pneumonectomy	1	..	..	1	
Subtotal gastrectomies	7	9	14	2	
Strumectomies	9	2	9	2	
Thoracoplasties	3	1	..	..	4
Uretherolithotomies	..	2	1	1	
Totals	45	35	62	14	4

* Cases shown in Medium column were treated in the second 24 hours by one more intravenous procaine injection, 10 to 20 cc. of 1 per cent solution, injected slowly in 4 to 5 minutes.

6. The general condition of patients receiving intravenous procaine for postoperative analgesia was better than that of those treated with morphine.

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GANGLIONEUROMA OF THE NODOSE GANGLION OF THE VAGUS*

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GANGLIONEUROMA is a relatively uncommon tumor in any location. It has only once previously been reported arising in the vagus nerve, and the present report records the first surgical removal of such a lesion.

The ganglioneuroma is the most highly differentiated tumor of neurogenic origin. Its histologic characteristics are the presence of large ganglion cells, sometimes multinucleated and often containing Nissl substance, and the presence of tangles or bundles of nerve fibers stainable by silver impregnation methods. Finely granular calcification and cystic changes may occur.[1] This type of tumor was first reported by Loretz,[2] who, in 1870, observed at autopsy such a lesion of an intercostal nerve, probably at the spinal or sympathetic ganglion. In the nearly 80 years that have elapsed since that report, many such tumors have been recognized in all parts of the body where ganglion cells might be expected. Roughly two thirds of the tumors involve the adrenals or abdominal sympathetic nerves or ganglia and most of the remaining one third arise in the cervical or thoracic sympathetic nerves. Still, McFarland and Sappington,[3] in a collective review, found records of ganglioneuroma involving the extremities, facial tissues, and cranial ganglia as well.

Ganglioneuroma arising in the cervical region is so uncommon that Shumacker and Lawrence,[4] in reporting such a case in 1939, could find records of only 13 previous patients who had such tumors in the neck. These authors pointed out that the proper preoperative diagnosis had never been made, although the collected cases had many features in common: slow growth, usually asymptomatic, generally from early childhood; freedom of overlying skin, but relative fixation of the tumor to the deeper structures; and displacement of the carotid artery to an anterior and superficial position. In only half the reported cases of cervical ganglioneuroma has the position of the carotid artery been recorded, and the finding of anterior displacement to a superficial position has been uniform in these.

Since the report of Shumacker and Lawrence, two additional reports of cervical ganglioneuroma have appeared in the literature. Foster[5] reported a case in 1942 of a 22-year-old woman who for many years had noted a tumor protruding into the left side of the pharynx. The tumor was easily removed through the pharyngeal mucosa. Histologically this tumor seems to have been a ganglioneuroma, though its exact site of origin is uncertain. In 1944 Bosse, Soffel, Nettrour, and Rohm[6] reported the removal of a ganglioneuroma from beneath the sternocleidomastoid muscle of a five and a half-year-old child. The operation was followed by ptosis for six months. This complication was also

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described in seven of the cases collected by Shumacker and Lawrence, and, when present, obviously indicates injury to the cervical sympathetics.

In 13 of the 14 patients collected by Shumacker and Lawrence, as well as in the two patients since reported, the ganglioneuroma seems to have arisen from the cervical sympathetic chain. Benda[7] reported in 1904 the only case prior to the present report in which the ganglioneuroma arose from the nodose ganglion of the vagus nerve. A colleague sent Benda an apple-sized specimen said to have come from an inoperable tumor in the right side of the neck of a child. It was not stated whether or not it was a surgical or an autopsy specimen, nor was the cause of death, if it was the latter, stated. This tumor lay in the right vagus trunk, with its lower extremity 3 cm. above the origin of the recurrent nerve. The cephalic end of the tumor was apparently not sent to the pathologist, but he was able to state that the origin of the tumor was in "the ganglion of the vagus." Histologically the tumor was a ganglioneuroma. The following case bears a striking similarity to Benda's.

FIG. 1.—Preoperative photograph showing left cervical mass.

Case Report.—*History.* J. S. (Unit No. 483125), a two and one-half-year-old white girl, was admitted to the surgical service of the Johns Hopkins Hospital on December 4, 1948, because of a swelling in the neck. Birth and early development were not remarkable, but when the baby was 8 months old she developed a fever and cough which subsided during a week of sulfonamide therapy. The physician who attended the child in this episode pointed out a left cervical swelling previously unnoticed by the parents. The swelling persisted but remained asymptomatic. There were never any signs of inflammation. The mother thought it had become a little larger in the month prior to admission. Because of this persistent swelling the child was brought to the pediatric outpatient department whence she was admitted to the surgical service.

Examination. The child showed no abnormality other than an enlargement of the left side of the neck, beneath the mandibular angle, more prominent when she looked to the right (Fig. 1). A firm, non-tender mass could be palpated deep in the neck beneath the left sternomastoid muscle. It measured about 5 by 7 cm. and was somewhat movable in a lateral direction. A striking feature was the marked displacement of the left carotid artery anteriorly and laterally so that this vessel appeared to be very superficial. The trachea was deviated somewhat to the right. There was no obstruction to breathing or swallowing and no limitation of motion of the head and neck. Roentgenograms confirmed the tracheal displacement but showed no calcification in the region of the mass.

Various possible diagnoses were considered, including hygroma and branchial cleft

cyst. Finally Dr. M. M. Ravitch suggested on the basis of the displacement of the carotid artery that the tumor was a neurogenic one arising paravertebrally.

Operation. On December 8, 1948, under ether anesthesia, a vertical cervical incision was made over the left sternomastoid, with a lateral extension along the supraclavicular region (Fig. 5). This permitted elevation of a flap of skin and platysma, division of the sternomastoid, and reflection of its upper segment. This gave excellent exposure. The tumor was found to be even larger than anticipated; it lay inside the carotid sheath and widely separated the internal jugular vein from the common carotid artery. When the carotid sheath was opened the tumor was seen to involve the vagus nerve, which ran upward on its surface for several centimeters. For much of this distance the vagus could

FIG. 2.—Photograph taken at operation showing vagus nerve, about which a tape has been placed, blending with the tumor above. The sternomastoid muscle has been divided and reflected. Its origin from the clavicle can be seen at the left.

be separated by blunt dissection from the tumor, but for a distance of about 2 cm. the vagus nerve actually gave origin to the tumor and was unrecognizable as a separate structure (Fig. 2). After this 2 cm. gap, the vagus again emerged from the mass and could be dissected free up to the jugular foramen, a distance of about one and one-half cm. The vagus nerve was injected with procaine above and below the tumor and divided at the points of fusion with the tumor, which could then be almost bloodlessly lifted out of the carotid sheath. No change in cardiorespiratory activity was detectable on injection or division of the left vagus nerve. The tumor thus arose in the nodose ganglion of the vagus, exactly as in Benda's patient. The vagus nerve had been so stretched and elongated by the devious course imposed upon it by the mass that with a minimum of retroclavicular mobilization of the lower segment the ends fell together easily. They were anastomosed without tension with 00000 silk sutures in the perineurium, and as nearly without rotation as could be determined.

Pathologic Examination. The specimen was a smooth, encapsulated ovoid tumor 8 cm. long, and 4 cm. in maximum diameter. The attached vagus nerve blended inseparably with one surface for two and one-half cm. (Fig. 3). The cut surface was white, homogeneous, and slightly lobulated (Fig. 3). Microscopically there were bundles and masses of nerve fibers passing both in and across the plane of the section, and scattered about were nests of large ganglion cells with large, occasionally multiple, nuclei, many of

which contained nucleoli. There were rare flecks of calcium. The tumor was a typical ganglioneuroma (Fig. 4).

Postoperative Course. The child's pulse rate, which varied from 100 to 140 before operation was as high as 170 on the afternoon of operation, falling gradually to preoperative range in 4 days. The wound healed per primam, and except for the hoarseness occasioned by paralysis of the left vocal cord, the only further complication was a

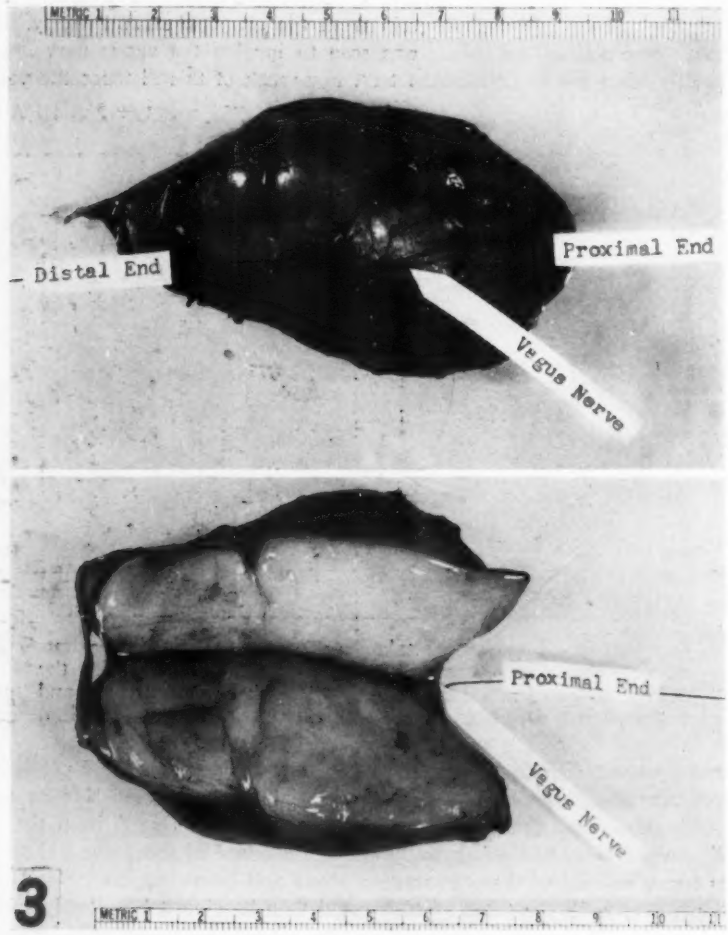

FIG. 3.—Photograph of the resected specimen. Ligatures mark the ends of the vagus nerve as it emerges from the tumor.

Horner's syndrome which cleared before discharge and must have resulted from operative trauma to the cervical sympathetics. The child has been well since leaving the hospital on December 17, 1948, nine days after operation. A photograph (Fig. 5) made 5 weeks after operation shows the healed incision. There was good motion of the head but some trapezius weakness persisted. Repeated laryngoscopic examinations were made, but as late as 9 months after operation there was still a complete left vocal cord palsy.

DISCUSSION

Ganglioneuroma is a slowly growing neoplasm, usually relatively free from surrounding tissue, a factor which simplifies its surgical removal. Pressure on

neighboring structures produces the deleterious effects; the removal of such a lesion from the neck thus becomes all the more imperative. Admittedly the clinical diagnosis of the precise histologic character of such a tumor is difficult, but a deep lateral cervical mass, relatively fixed, but free from overlying skin and displacing the carotid artery anterolaterally, is likely to be a neurogenic tumor arising paravertebrally. There is no ready method for distinguishing clinically between a neurinoma and a ganglioneuroma, nor can it be determined before exploration whether the origin of the tumor is from cervical sympathetic chain, vagus trunk, or from accessory or hypoglossal or other nerves in this location.

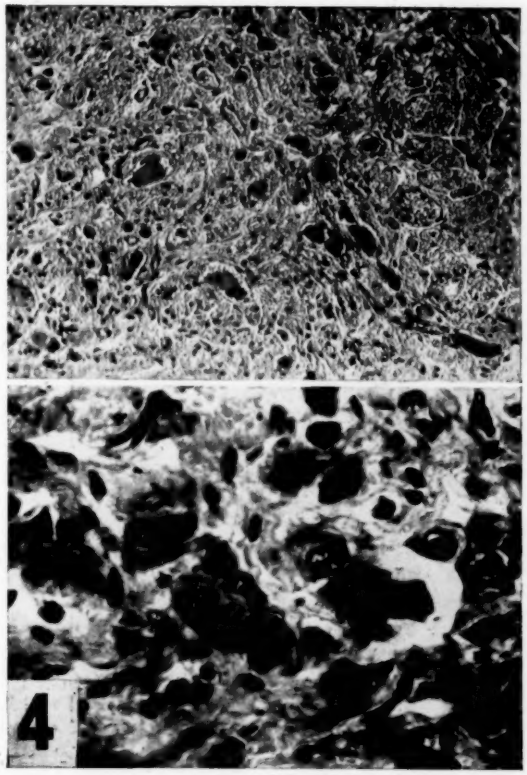

FIG. 4.—Low and high power photomicrographs of tumor, a ganglioneuroma. Note nerve fibers in bundles and large mature ganglion cells.

It is noteworthy in the present case that neither procaine injection into the left vagus nerve nor section of its cervical portion under ether anesthesia had any demonstrable effect on the cardiorespiratory function. There was, however, some postoperative tachycardia lasting four days. It is doubtful that this was more marked than would be expected in a child of this age who had undergone any large operative procedure. This is in general agreement with the findings of the various authors who have previously reported resection of the cervical portion of one vagus. This operation has been recorded in seven previous instances for removal of various tumors involving the vagus. According to reports, three of the patients had neurinoma (or neurofibroma),[8-10] one had "neurinoma sarcomatodes,"[11] another spindle cell sarcoma,[12] and yet another paraganglioma.[13] The tumor in the seventh patient was not examined histologically.[12] In only one of the patients[12] was there any disturbance of cardiorespiratory or gastro-intestinal function associated with division of the vagus, and most authors commented specifically on the absence of such effect. Postoperative vocal cord paralysis was, of course, a constant finding in these patients. Suture of the nerve was not attempted in any case.

While insufficient time has elapsed to determine the ultimate success of the

suture of the divided vagus in the present instance, it seems unlikely that the cord will regain its motility. However careful one may be to re-approximate the ends of the vagus nerve without rotation, it appears improbable that one could so place them that the proximal fibers intended to innervate the intrinsic laryngeal musculature would regenerate down the appropriate neurilemmal sheaths to turn back in the recurrent nerve.

SUMMARY

1. Ganglioneuroma is a rare tumor in the neck. In this location it usually arises from the cervical sympathetic ganglia.

2. A ganglioneuroma of the nodose ganglion of the vagus nerve has been successfully removed from a two and a half-year-old child.

3. Resection of the nerve caused no difficulty except a paralysis of the ipsilateral vocal cord which persists nine months after primary neurorrhaphy.

FIG. 5.—Postoperative photograph showing scar of healed incision.

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DIVERTICULITIS OF THE JEJUNUM*

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DIVERTICULA OF THE JEJUNUM are rare. The frequency of diverticula in the various portions of the alimentary tract as indicated by Fraser[11] is as follows: first, colon; second, ileum (Meckel's diverticulum); third, duodenum; fourth, pharynx and esophagus; fifth, stomach; and sixth, jejunum. Those occurring in the jejunum are most often found near the ligament of Treitz and these diminish distally in size and number. They usually occur as herniations of the mucous membrane through the muscular coat of the intestinal wall (false diverticula) and protrude through openings between the mesenteric leaves at the points of vascular perforations. Their sizes vary greatly, some being as large as an orange. A single diverticulum, or as many as 500 may be found.

Sir Astley Cooper[7] in 1844 was apparently the first to report jejunal diverticula. These were found at autopsy. Most of the early cases were discovered in this manner. Sir William Osler[21] in 1881 described a male patient who showed 53 jejunal diverticula as an incidental autopsy finding. More recently, a considerable number of jejunal diverticula have been found during the course of abdominal operations performed for conditions unrelated to the diverticula. A few have been discovered at operation for the relief of symptoms due to the diverticula.

Discovery by roentgenographic examination has occasionally been made since 1920, when Case[4] made the diagnosis by this method. This method is not very reliable, as jejunal diverticula found, but not removed, at operation often fail to visualize radiographically after the operation. Rankin[23] reported that in 956 stasis or serial roentgen ray examinations of the small intestine three instances of jejunal diverticula were seen. Until 1932 at the Mayo Clinic jejunal diverticula were found in 41 patients. All were discovered by roentgenography or incidentally at autopsy or operation. At no time did a patient undergo surgery for relief of symptoms thought to be due to diverticula. Other authors who have arrived at the diagnosis by roentgenographic study are Braithwaite,[2] Cook and Hunt,[6] Edwards,[8] and Jenkinson.[18]

The exact frequency of jejunal diverticula is rather difficult to estimate. Gerster's[12] bibliography cites 128 references recording 187 cases from 1844 (Cooper) to 1938. Since then cases have been reported by Ovens[22] (one case), Hubeny and Pollack[17] (one case), Shutkin[26] (one case), and Mahorner and Kisner[20] (two cases). With the exception of these authors all the references cited in our bibliography are included by Gerster and contribute to his total number of cases.

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Rosedale[25] reported three cases of multiple jejunal diverticula among 5000 autopsies. Later, as a result of routine insufflation of the small intestine *in situ* under moderate air pressure, four cases among 300 autopsies were discovered. Edwards[8] reported nine instances in 2800 autopsies.

Symptoms may be absent, or vague digestive disturbances may be observed. Edwards[8] described "flatulent dyspepsia" occurring with jejunal diverticulosis. Patients exhibiting hemorrhage have been recorded by Guthrie[16] and Tengwall.[28] Obstructions due to enteroliths or adhesions have been reported by Christ,[5] Renaud,[24] Terry and Mugler,[29] Watson,[30] Hubeny and Pollack,[17] Fort,[10] Kaspar,[19] Boling,[1] and Godard.[13]

FIG. 1.—Postoperative roentgenogram of upper jejunum showing two remaining diverticula.

Inflammatory changes have been reported in a small number of cases. These have included diverticulitis with and without perforation. Some of the patients had preceding symptoms for a varying length of time and others exhibited a sudden onset without previous symptoms. Peritonitis due to perforation of an acutely inflamed diverticulum was noted by Fraser,[11] Gerster,[12] Butler[3] (three cases), Shutkin,[26] Fagge,[9] and Spackman.[27] Acute diverticulitis without perforation was discovered at operation by Edwards,[8] Gordinier and Sampson[15]; and in Goinard's[14] case, inflammation and the ova of Strongyloides intestinalis were found in the diverticulum.

Our case is an example of jejunal diverticulitis without perforation. Diverticulosis was also present. The onset was sudden with no pre-existing gastro-intestinal symptoms. Postoperatively, two remaining upper jejunal diverticula were demonstrated in the roentgenogram (Fig. 1).

CASE REPORT

Mrs. V. F., married housewife, white, age 39, hospital number 49-3756 was admitted to the hospital on March 20, 1949, at 10:45 P.M.

Twenty-six hours before admission she noticed pain to the left of the umbilicus which was constant after its onset and which became progressively more severe. Anorexia accompanied the pain, and vomiting occurred once. A self-administered enema had produced no relief. Standing, sitting, or lying on either side aggravated the pain. A menstrual period began the day before the onset of the pain.

The past history disclosed that a diagnosis of uterine fibroids had been made 3 years

before. Appendectomy had been performed in 1934. Six pregnancies with 5 living children had occurred.

Physical examination disclosed a slender, pale woman who appeared acutely ill. The temperature was 101°F., pulse rate was 110, and the blood pressure was 128/80. The abdomen showed marked tenderness and rebound tenderness in the left lower quadrant. A questionable mass in this area was palpated. Peristaltic sounds were markedly diminished. No rigidity was noted. Vaginal examination revealed the uterus to be slightly larger than normal size. It was retrodisplaced and boggy. No fibroids or adnexal masses were palpated. Rectal examination was non-contributory.

Roentgenograms of the chest and abdomen revealed no abnormal changes.

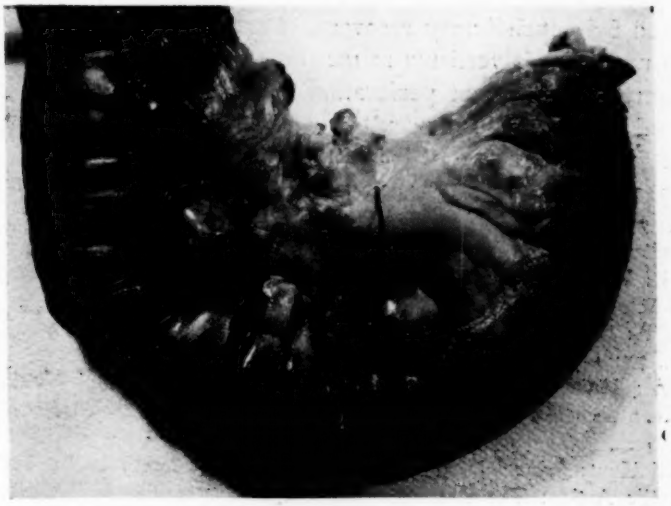

FIG. 2.—Section of removed jejunum showing diverticula. Arrow points to area of inflammation. Jejunal segment is slightly distended with water and closed at both ends to demonstrate diverticula more satisfactorily.

The laboratory examination showed a leukocytosis of 20,550 with 9370 segmented cells. The urine was within normal limits.

A diagnosis of an acute surgical abdomen of doubtful etiology was made. Abdominal exploration was recommended and performed.

The operation was performed through a lower abdominal mid-line incision. The peritoneal cavity contained a moderate amount of yellowish-green exudate. The surfaces of the small intestine were hyperemic. A loop of jejunum about 6 inches long was distended and edematous. This segment of jejunum was approximately 22 inches from the ligament of Treitz. It was plastered together by recent fibrinous adhesions in the shape of a "U." The adjacent mesentery was extremely thick and edematous, and in one area was about to perforate. Along the nearby non-inflamed jejunum, both proximally and distally, were probably 15 to 20 diverticula, varying in size, on the mesenteric border of the small intestine. The cecum was greatly distended and a fibroid about the size of a cherry was present in the uterine fundus.

Twelve inches of jejunum, including the area of inflammatory change, were resected. A number of the non-inflamed adjacent diverticula were removed in the resected segment (Fig. 2). An end-to-end anastomosis was then performed. When the wall of the inflamed diverticulum was opened, about 30 cc. of frank pus was evident. Sections from this area revealed acute inflammation.

A very satisfactory postoperative recovery followed. One blood transfusion of 500 cc. was given immediately following surgery. Wangensteen suction was instituted after the operation and discontinued after 2 days. The highest postoperative temperature was 100.2°F. The patient was discharged from the hospital on the ninth postoperative day and has remained well since then.

Cultures of the peritoneal exudate obtained at operation showed no bacterial growth. A direct smear of the exudate revealed some red blood cells and pus cells but no bacteria.

SUMMARY

A case of jejunal diverticulitis producing an acute surgical abdomen is reported. Jejunal diverticulosis was also present. Resection of the jejunum was followed by a satisfactory recovery. Postoperative roentgenograms disclosed two remaining diverticula in the upper jejunum. Only a few cases of jejunal diverticulitis without perforation have been reported.

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BOOK REVIEW

REVIEW OF RECENT ADVANCES IN ANESTHESIA AND ANALGESIA. By C. Langton Hewer, M.D., Sixth Edition, 1948, Blakiston, Philadelphia.

Four years have elapsed since the fifth edition of this book. The present edition contains much recent information. The book is divided into 28 chapters with index following, giving the theoretical aspects of inhalation anesthesia and premedication. There are chapters on the various anesthetic agents, operative risk in anesthesia, intravenous anesthesia, the muscular relaxants, several chapters on local anesthesia, a chapter on spinal anesthesia, and on collapse and resuscitation. Doctor Hewer discusses anesthesia for neurosurgery, dental surgery, macilo-facial surgery, thyroid surgery, thoracic surgery, abdominal surgery, and anesthesia in obstetrics, including resuscitation of the newborn.

It might be noted that in the chapter on nitrous oxide and the hydro-carbon gases, Doctor Hewer makes a statement that pure nitrous oxide-oxygen is used extensively in America for major surgery, and intimates that the toxicity of oxygen lack is perhaps more fully appreciated in Great Britain. It must be stated here that the toxicity of oxygen lack is fully realized in America, and that surely all the anesthesiologists of this country are "hypoxia conscious."

In the chapter on analeptics, Doctor Hewer leads one to believe that coramine and drugs like it are advantageous in respiratory depression. We would like to point out that coramine and the entire group of respiratory stimulants are of no value when respiratory depression is severe. In the chapter on spinal anesthesia, the author frowns on taking blood pressures too often in the conscious patient and minimizes the value of the blood pressure reading in favor of the patient's color and characteristics of his pulse. We certainly feel that frequent blood pressure readings will give the trend of what may be happening to the circulatory system long before the patient's color or pulse becomes a reliable sign.

Doctor Hewer concludes his book with a consideration of anesthetic sequelae and a final chapter on anesthetic records on charts. This book is well put together and is a tremendous source for reference on each subject presented. Illustrations are both good and numerous.

JOSEPH F. ARTUSIO, JR., M.D.

Editorial . . .

The Problem of Thrombo-embolism

The voluminous literature which has accumulated during the past decade on the subject of thrombo-embolism clearly reflects the intensive and widespread interest in this problem and the energetic efforts directed toward its control. To be sure, additional knowledge has been provided by these studies, but a review of this literature reveals much confusion and bewilderment, as evinced by the wide discrepancy and the great variability in the reported incidence of the condition, in the concepts of its pathogenesis, in the descriptions of its clinical picture, and especially in the measures proposed for its prevention and treatment. The methods suggested for both prophylaxis and therapy range from simple conservative measures to radical operative intervention, with the advocates of each procedure claiming efficacy by supporting data. And now, just when it would seem from these publications that the problem is finally being brought under control, more recent reports from institutions where the condition has been under intensive study reveal that despite these assiduous efforts the incidence of thrombo-embolism, and even of fatal pulmonary embolism, has continued to increase. These disconcerting observations serve to heighten rather than diminish the confusion and thus lend further emphasis to the need for a closer scrutiny and a more critical evaluation of the problem.

A number of factors have probably contributed to this state of confusion. Most important are the lack of precise knowledge concerning the etiology and pathogenesis of the disease, its protean nature, and the frequent difficulties involved in the establishment of the diagnosis. This latter consideration is especially important and undoubtedly plays a highly significant role in determining incidence and consequently in evaluating therapy.

The significance of incidence in the evaluation of the various methods advocated for prophylaxis and therapy in thrombo-embolism may be readily illustrated by a random selection of recent reports on the subject. For example, in one institution in this country in which a routine prophylactic anticoagulation (Dicumarol) program had been adopted for surgical patients over a four-year period, the incidence of fatal pulmonary embolism was about 1 in 3000 surgical cases. In a presumably comparable untreated series of surgical cases, it was about 1 in 400. On this basis, the conclusion was drawn that this method of prophylaxis seemed efficacious. But this apparently lowered incidence does not differ materially from that recently reported from two other institutions which do not employ such a routine prophylactic program and in which the respective incidences for fatal pulmonary embolism were approximately 1 in 2700 and 1 in 2000 surgical cases. Since season and climate have been considered as factors accounting for some of the discrepancy in the reported incidences, it is interesting to note that one of these institutions is located in the deep South and the other in the North.

Another significant aspect of incidence lies in its usefulness as a means of estimating the value and the disadvantages of a particular method of prophylaxis or therapy against the actual hazards of the disease. For example, in a recent report on the use of Dicumarol prophylactically following operation there were no fatalities from pulmonary embolism in almost a thousand cases but there were two deaths from hemorrhage, which seems to suggest that the dangers associated with this method of prophylaxis equal, if they do not exceed, the actual hazards of the disease. If the chances of death from the disease and from its method of prophylaxis are equal, one might readily choose the former since it is usually quicker and certainly cheaper.

From these observations it is clear that an accurate determination of incidence constitutes a crucially important factor in evaluating both prophylaxis and therapy in thrombo-embolism. But an accurate determination of incidence depends, in turn, upon accuracy in diagnosis, and herein lies the major difficulty. In a high proportion of cases—this is especially true in so-called bland thrombosis or phlebothrombosis—the diagnosis may be little more than an assumption based upon a high degree of suspicion and upon clinical criteria that are often vague and indefinite. Moreover, in many of these cases unless thrombosis or embolism is actually demonstrated at operation or at necropsy, the diagnosis can never be definitely established. Even when the classical manifestations of pulmonary embolism are present, subsequent necropsy may prove the clinical diagnosis to be erroneous. It is apparent, therefore, that the clinical diagnosis of thrombo-embolism will be made with varying frequency, depending upon the manner in which the clinical criteria are interpreted, and that the interpretation will, in turn, depend in great measure upon the awareness, interest, and enthusiasm of the observer. In institutions where there is a keen interest in the problem, and especially where a particular method of prophylaxis and therapy is being studied, there obviously exists a greater awareness of the condition, and consequently a higher index of suspicion in the minds of the observers, than in institutions where such conditions do not prevail. An attitude of suspicion, of course, may make for earlier diagnosis, and perhaps for better management, but it may also lead to the making of the diagnosis more frequently than it actually exists. Moreover, since in a high proportion of cases there is no definitive means of confirming or refuting it, this margin of error cannot be accurately ascertained. For example, under conditions where a high degree of suspicion exists, the diagnosis of phlebothrombosis may be made on the basis of rather vague findings, such as slight changes in the temperature and pulse rate not otherwise to be explained and slight tenderness in the calf. Following the institution of therapy by ligation or by anticoagulants, depending upon the special interest of the observer, there is complete recovery and another case of thrombo-embolism is placed upon the records. In a sense, the diagnosis has been made on suspicion and confirmed by therapy. In other institutions, where a comparable interest in the problem does not exist, similar manifestations may go unnoticed and, if no further developments occur, the diagnosis is never recorded. Since there is no way of

definitely establishing the diagnosis under these circumstances, there is no way of determining the margin of error that exists in making it.

As a consequence of the variability in the recording of the diagnosis and in its accuracy, considerable difficulty is encountered in assessing the results of a particular form of therapy on the basis of a statistical analysis of such records. Despite its significance this factor has not been fully appreciated. This is well exemplified by the numerous articles in the recent literature in which conclusions are drawn concerning the value of a particular form of prophylaxis or therapy from an analysis of just such data as these. In some instances even refined methods of statistical analysis have been employed to demonstrate significance when the accuracy of the basic data remains questionable.

It is thus apparent that much of the confusion which now prevails in the literature on the subject of thrombo-embolism stems from the difficulty of establishing a firm base line for the disease. It would also appear that some of it arises from an inadequate appreciation of this fact, reflecting the need for a more critical attitude toward this problem. The solution to the first of these difficulties lies in the development of a more accurate means of diagnosis. The solution to the second is more readily available. It merely involves the more rigid application of the principles and methods which should characterize the scientific approach to any problem, as emphasized in a recent editorial in this journal. Further efforts directed toward these objectives may lead to a better understanding of the problem of thrombo-embolism, and perhaps to its effective control.

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